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(21) International Application N (22) International Filing Date: (30) Priority data: 731,563 1 870,975 2	92) (75) Inverse (	(72) Inventors; and (75) Inventors; Applicants (for US only): CARR, Thomas, Joseph [US/US]; 1232 Harrison Avenue, Phoenixville, PA 19460 (US). DeMARSH, Peter, Lawrence [US/US]; 20: Armstead Court, Downington, PA 19335 (US). DREY ER, Goeffrey, Bainbridge [US/US]; 2 Marlin Drive Marlvern, PA 19355 (US). FENWICK, Ashloy, Edward [GB/US]; 115 Pine Tree Road, Radnor, PA 19087 (US).					
(60) Parent Applications or Grants (63) Related by Continuation US Filed on 19 April 1992 (19.04.92) US Filed on 17 July 1991 (17.07.91) (71) Applicant (for all designated States except US): SMITH- KLINE BEECHAM CORPORATION [US/US]; Corporate Patents-U.S., UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).  (74) Agents: KINZIG, Charles, M. et al.; SmithKline Beec Corporation, Corporate Patents - U.S., UW2220, Swedeland Road, P.O. Box 1538, King of Prussia 19406-0939 (US).  (81) Designated States: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MN, MW, NL, NO, PL, RO, RU, SD, SE, US, 1, TL, UM, MC, NL, SE), OAPI patent (BF, BI, CF, CI, CM, GA, GN, ML, MR, SN, TD, TG).							
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### Background of the Invention

The present invention relates to retroviral protease

10 inhibitor compounds, pharmaceutical compositions thereof, and
a method of treating retroviral diseases therewith, including
a method of treating disease states associated with human
immunodeficiency virus (HIV-1, HIV-2).

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(acquired immunodeficiency syndrome) and AIDS related complexes, and many others. Although the pathogens have, in many of these cases, been isolated, no effective method for treating this type of infection has been developed.

Retroviral replication occurs only in host cells. Critical to this replication is the production of functional viral proteins. Protein synthesis is accomplished by translation of the appropriate open reading frames into polyprotein constructs, which are processed, at least in part, by a viral protease into the functional proteins. proteolytic activity provided by the viral protease in processing the polyproteins cannot be provided by the host and is essential to the life cycle of the retrovirus. In fact, it has been demonstrated that retroviruses which lack the protease or contain a mutated form of it, lack infectivity. See Katoh et al., Virology, 145, 280-92(1985), Crawford, et al., J. Virol., 53, 899-907 (1985) and Debouk, et al., Proc. Natl. Acad. Sci. USA, 84, 8903-6(1987). Inhibition of retroviral protease, therefore, presents a method of therapy for retroviral disease.

The use of isosteric replacements has been disclosed as a strategy for the development of protease inhibitors for HIV-1. European Patent Applications EP-A 337,714, EP-A 357 332, EP-A 346 847, EP-A 342 541, EP-A 352 000, EP-A 393 445 and EP-A 434 365 are representative, and are incorporated herein by reference. These references disclose dipeptide analogs of the natural polyprotein substrates of retroviral proteases. As discussed therein, these dipeptide analogs bind selectively and competitively to retroviral proteases; however, the protease is unable to cleave the carbon-carbon bond presented to it instead of the scissile amide bond of the natural substrate. Thus, such compounds are useful for inhibiting viral replication by inactivation of the protease. The incorporation of heterocyclic elements in the P3' and P4' substrate positions of compounds containing a dipeptide isostere has been disclosed by deSolms et al., J. Med. Chem., 34, 2852 (1991). However, these compounds can be less than desirable for obtaining optimal drug delivery in mammalian

organisms, particularly in humans. Some of these compounds can also have a less than desirable serum half-life, and therefore duration of action, because they contain amide bonds in relatively high proportion, and thus are prone to metabolic degradation, hepatic clearance, or other elimination mechanisms.

There exists a need for novel compounds which inhibit retroviral protease activity, and a need for compounds which possess desirable pharmacokinetic properties for good drug delivery and metabolic stability for good serum half-life and duration of action. Such pharmaceutical uses provide therapies for retroviral diseases in mammals, especially in humans, which have been heretofore difficult to treat.

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#### SUMMARY OF THE INVENTION

The present invention provides compounds, hereinafter represented as formula (I), which bind to retroviral proteases. These compounds are inhibitors of retroviral proteases and are useful for treating diseases related to infection by retroviruses.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

The present invention additionally provides a method for treating retroviral disease, comprising administering to a mammal in need thereof an effective amount of a compound of 

# 30 (CMD) O COMPANY DETAILED DESCRIPTION OF THE INVENTION

odd to Jew The compounds of the present invention are illustrated by formula (I):

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R1 and R3 are each independently Q, Q-C1-6alkyl, Q-C2-6alkenyl, Q-C2-6alkynyl or C1-6alkyl substituted by one to five fluorine atoms, each optionally substituted by R23; Q is H, C3-6cycloalkyl, C5-6cycloalkenyl, Ar or Het

R2 is H or OH; and a Location bin washing be

R5 is R6-NR11\_ or R102NR11\_; or see or settler if

X is NR<sup>11</sup>, O or S;

 $R^7$  is Q, Q-C<sub>1-6</sub>alkyl or Q-C<sub>2-6</sub>alkenyl;

 $R^8$  and  $R^9$  are each independently H, OH, halo,  $NO_2$ ,  $COR^{12}$ , CF<sub>3</sub>, Ar, C<sub>1-6</sub>alkyl-R<sup>15</sup>, or R<sup>17</sup>(R<sup>18</sup>R<sup>19</sup>C)<sub>m</sub>, or together form a fused C2-4alkylene, aryl or heteroaryl moiety;

 $R^{10}$  is  $A-(B)_{n}-;$ 

R11 is H or C1-4alkyl;

R12 is R7, OR7, NR7R11 or an amino acid or amino alcohol;

B is an amino acid; the decomposite

A is H, Ar, Het,  $R^{17}(R^{18}R^{19}C)_{m}$ , Ar-W, Het-W or , R17 (R18R19C) m-W, or phthaloyl each optionally substituted by one to three groups chosen from R15 or C1-6alkyl-R15;

W is C=0, OC (=0), NR<sup>11</sup>C(=0), SC(=0), NR<sup>11</sup>C(=S), SO<sub>2</sub>,

 $NR^{11}SO_2$  or P(=0) ( $OR^{22}$ );

R15 is H, nitro, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkylthio, O(C=O)R16, C=OR<sup>22</sup>, CO<sub>2</sub>R<sup>22</sup>, CON (R<sup>16</sup>)<sub>2</sub>, N(R<sup>22</sup>)<sub>2</sub>, NHC (=N) NH-A, I, Br, Cl, F, OR10, or OH, provided that when R15 is a substituent of the carbon adjacent to W, R15 is not halogen or OH when W is OC (=O) or NHCO;

R16 is H or C1-6alkyl;

 ${
m R}^{17}, {
m R}^{18}$  and  ${
m R}^{19}$  are independently: i) H,  ${
m R}^{15}$  or  $C_{1-4}$ alkyl,  $C_{2-6}$ alkenyl, phenyl, naphthyl,  $C_{3-6}$ cycloalkyl or Het, each optionally substituted by one to three R15 or

joined together to form a phenyl, naphthyl, C3-6cycloalkyl or Hetiring, or iii) R<sup>17</sup> is as above and R<sup>18</sup> and R<sup>19</sup> together are corecard =0;) of her happy was the mean and respectively.

 $R^{22} \text{ is}_{\text{H,9}} C_{1-6} \text{alkyl, phenyl or phenyl-} C_{1-4} \text{alkyl;}$   $R^{23} \text{ is}_{\text{-X'-(CH_2)}} \text{qNR}^{24} \text{R}^{25}, \text{X"[((CH_2)_rO)_8]} \text{R}^{26},$ 

The Roll azabicyclo C7-11cycloalkylmor benzopiperidinyl, optionally le anol substituted with C1-4alkyl;

dolo: It yeuq is 2-5; with but a far your

s is 1-6 and r is 1-3 within each repeating unit s;

(3) Sing X" is (CH<sub>2</sub>, NR', O, S, SO or SO<sub>2</sub>;

OR<sup>24</sup> and R<sup>25</sup> are i) C<sub>1-6</sub>alkyl, optionally substituted by

- OH, C1-3alkoxy, or N(R\*)2, ii) the same or different and joined together to form a 5-7 member heterocycle containing up to two additional heteroatoms selected from NR, 0, S, SO, SO2, said heterocycle optionally substituted with C1-4alkyl, iii) aromatic heterocycle, optionally substituted with
- 20 C1-4alkyl-or N(R')2; Layer ore of the best of the be-

walk!cis.Hor.C1-4alkyl; 0v a sy giv no giv no ac ci - A

 $R^{26}$  is H,  $C_{1-4}$ alkyl,  $C(=0)R^{27}$ ,  $C(=0)U[(CH_2)_mO]nR^4$ ,  $P(=0)(OM)_2$ ,  $CO_2R^{27}$ ,  $C(=0)NR^{27}R^{28}$ , where M is a mono or included inetal ion, and U is NR' or O;

R<sup>27</sup> is C<sub>1-6</sub>alkyl or Ar, optionally substituted with one or more hydroxy, carboxy, halo, C<sub>1-3</sub>alkoxy, CONR'<sub>2</sub>, NR'<sub>2</sub>, CO<sub>2</sub>R', SO<sub>2</sub>NR'<sub>2</sub>, CH<sub>2</sub>NR<sub>2</sub>, NR'COR', NR'SO<sub>2</sub>R', X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>R' or CH<sub>2</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>R'<sub>1</sub>, So<sub>2</sub>CH<sub>2</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>R'<sub>1</sub>, So<sub>2</sub>CH<sub>2</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>R'<sub>1</sub> So<sub>2</sub>CH<sub>2</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>R'<sub>1</sub> So<sub>2</sub>CH<sub>2</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>R'<sub>1</sub> So<sub>2</sub>CH<sub>2</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>R'<sub>1</sub> So<sub>2</sub>CH<sub>2</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>X"[(CH<sub>2</sub>)<sub>2</sub>O]<sub>8</sub>X

OFR<sup>28</sup> is H, C<sub>1</sub>-falkyl or together with R<sup>27</sup> forms a 5-7

30 [Ymembered heterocycle or a 6 membered heterocycle containing a heteroatom selected from N, O and S;

· m is 1-4; and

the mattern in is O'orth, 1909, the logar army to with a color

or a pharmaceutically acceptable salt thereof.

35 value Also included in this invention are pharmaceutically vacceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be

many covalently bonded carriers which refease the active parent drug according to formulat (I) intrivo. bester

rormula (I) is intended to encompass all unique
nonracemic stereoisomers which may occur due to the presence
of asymmetric carbon atoms in the molecule. Such compounds
may occur as pure enantiomers or diastereomers or as a
mixture of individual stereoisomers. The definition of any
substituent moiety which may occur more; than once in formula
(I) is independent of any other occurrence combinations of
substituents and/or variables are permissible only if such
combinations result in stable compounds:

Compounds of this invention which include acyclic double bonds may be present in either the cis (Z) or trans (E) geometrical configuration with respect to any two

15 substituents. The second of the xo we then in the

when X is NH, it will be appreciated that the characteristic ring is an imidazole which can undergo tautomerization. All tautomerics forms of the imidazole are within the scope of this invention.

Suitably R<sup>1</sup> and R<sup>3</sup> are C<sub>1-6</sub>alkyl, Ar-C<sub>1-6</sub>alkyl, S Ar-C<sub>2-6</sub>alkenyl, Ar-C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkyl optionally substituted by one to five fluorine atoms or benzyl substituted in the 4-position by R<sup>23</sup> Preferably R<sup>1</sup> is benzyl and R<sup>3</sup> is benzyl, 4-hydroxybenzyl, or phenylpropenyl.

Suitably R2 is H. . . . . . Lake spage at Take

Suitably X is S or N-R<sup>11</sup>. Preferably X is NH. To Preferably R<sup>4</sup> is CONR<sup>11</sup>CHR<sup>6</sup>R<sup>7</sup>. The Constant of the

Suitably R<sup>5</sup> is R<sup>10</sup>-NR<sup>11</sup>. Preferably R<sup>5</sup>c is to butyloxycarbonylamino or isopropyloxycarbonylamino.

Suitably R<sup>7</sup> is H, C<sub>1-6</sub>alkyl, C<sub>3-6</sub>cycloalkyl, phenyl or benzyl. Preferably R<sup>7</sup> is C<sub>1-6</sub>alkyl. Isopropyl is most preferred.

Suitably R<sup>8</sup> is H, C<sub>1-6</sub>alkyl, COR<sup>12</sup>, NO<sub>2</sub> or Br. Preferably R<sup>8</sup> is H.

Suitably R<sup>9</sup> is H, NO<sub>2</sub>, Br, COR<sup>12</sup>, CF<sub>3</sub>, Ar, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl-R<sup>15</sup>, wherein R<sup>12</sup> is H, C<sub>1-6</sub>alkyl, Ar, OC<sub>1-6</sub>alkyl, NH<sub>2</sub>, and R<sup>15</sup> is OH. Preferably R<sup>9</sup> is H or COR<sup>12</sup>

Figure Suitably B is Ala or Val. Preferably m is 0 and B is about absent, which is a figure of the state of t

Suitably A is Het, R17 (R18R19C) m-W, Ar-W or Het-W.

Suitably R17, R18 and R19 are H, or C1-4alkyl, Het or Ar

(R<sup>18</sup>R<sup>19</sup>C) are joind together to form a phenyl, C<sub>3</sub>-6cycloalkyl or Het ring.

Suitably W is C=O, OC(=O), NHC(=O), NHC(=S), or SC(C=O).
Suitably R<sup>17</sup>(R<sup>18</sup>R<sup>19</sup>C)<sub>m</sub>- is Ar-CH<sub>2</sub>, Ar, Het, Het-CH<sub>2</sub>,

- 10) C1-6alkyl or C3-6cycloalkyl optionally substituted by one to three groups selected from R15. Suitably R15 is OH. When R17 or (R18R19C) are Het or Ar, Het is suitably quinolinyl, pyridyl, imidazolyl, thiazolyl, tetrahydrothiopyranyl or tetrahydropyranyl and Ar is phenyl.
  - Suitably R<sup>23</sup> is hydroxy-C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxy-C<sub>1-4</sub>alkoxy, or -O(CH<sub>2</sub>)<sub>2</sub>NR<sup>24</sup>R<sup>25</sup>, wherein R<sup>24</sup> and R<sup>25</sup> are are a substantial or 6-membered heterocycle, such as morpholino.

    In one preferred embodiment W is C=O.

"1) "1 In another preferred embodiment W is OC (=0).

C5-6cycloalkylOC(=0) substituted by one or two OH or CH2OH

The groups.

Representative compounds of this invention are:
(2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-

25 amino-6-phenyl-N-[l'-isopropyl-1'-(4-aminocarbonyl-thiazo-2-yl)]methyl-hexanamide;

(2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) -

- 30 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
- ... () amino-6-phenyl-N-(1'-imidazo-2-yl)methyl-hexanamide

-i hydrochloride; was a second and a second a se

- -'; amino-6-phenyl-N-[1'-methyl-L'-(imidazo-2-yl)] methyl-
- 35 hexanamide hydrochloride;

  (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-benzyl-1'-(imidazo-2-yl)]methylhexanamide hydrochloride;

```
(2R, 4S, 5S, 1'S) -5- (carbobenzyloxy) amino-4-hydroxy-N-(1'-
        isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                            Settebly A is Me. of the Co
        hexanamide:
        (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
    5 isopropyl-1'-(4,5-dimethyl)imidazol-2-yl]methyl-6-phenyl-2-
      P phenylmethyl-hexanamide; of special miles by a (38 48 4)
        (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
       isopropyl-1'-(N'-methyl)imidazol-2-yl]methyl-6-phenyl-2-
      phenylmethyl-hexanamide: m((181, 2)(1)) 12 (168)
       (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy'N-(1'-
       isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3->=0
       phenylpropargyl) hexanamide; 3 1 3 27 213 (53 (53 ) uc
       (2R, 4S, 5S, 1'S) -5- (benzyloxyethoxycarbonyl) amino-4-hydroxy-N-
       (1'-isopropyl-1'-imidazol-2-yl)methýl-6-phenyl-2-10:
      phenylmethyl-hexanamide; which at Ala yak and yet
       (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
      hexanamide;
                            the flux many respectively earliest
       (2R, 4S, 5S, 1'S) -5-(ethoxycarbonyl) amino-4-hydroxy-N-(1'-
(C20 ) isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
      hexanamide:
                                     on a functionary many or mago
      (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-
      propenyl) hexanamide; "see Eyes outs assign $5 (85 5 \ 5 1,23 1,33)
 25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
      isopropyl-1'-(4-nitroimidazol-2-y1)]methyl-6-phenyl-2-
  phenylmethyl-hexanamide;
      (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
     ethyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
     hexanamide; " " " " " " " " " I' " " sale maniq-S- (2° 5 (pe (0)) all
     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
     propyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                   more the well the english and good ($1 type, 20), and
    (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
     isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-
     phenylmethyl-hexanamide; discrete property of the phenylmethyl-hexanamide;
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(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
        isopropyl-1!-(4,5-dibromoimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide; b at the fifty of the first of the
   (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
 cols ( isopropyl=1%-(4-methylimidazol=2-yl) ]methyl=6-phenyl=2-
       phenylmethyl-hexanamide; with we are compact
-1; -' 1: (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
        isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-
       phenyl-2-phenylmethyl-hexanamide; name of the end of the
10 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-methyl-
 [vd == N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
       phenylmethyl-hexanamide;
  (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
       isopropyl-1'-(4-carbomethoxyimidazol-2-yl)]methyl-6-phenyl-2-
   15 .phenylmethyl-hexanamide;
                                     anto o escorptionas au est
       (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
   -9->isopropyl-1!-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-
       2-phenylmethyl-hexanamide;
   (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
       isopropyl-1'-(4-phenylcarbonyl-imidazol-2-yl)]methyl-6-
       phenyl-2-phenylmethyl-hexanamide;
 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
 isopropyl-1'-(4-formylimidazol-2-yl)]methyl-6-phenyl-2-
       phenylmethyl-hexanamide;
  25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
       isopropyl-1'-(4-(hydroxymethyl)-imidazol-2-yl)]methyl-6-
    the phenyl-2-phenylmethyl-hexanamide;
   (2R, 4S, 5S, 1'S) -5- ((tetrahydrothiopyran-4-yl) oxycarbonyl) -
     amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
  30 phenyl-2-phenylmethyl-hexanamide; 33 phenyl-2-phenylmethyl-hexanamide;
     - (2R,4S,5S,11S)-5-((tetrahydro-4H-pyran-4-yl)oxycarbonyl)-
 -3-14 amino-4-hydroxy-N-(1!-isopropyl-1'-imidazol-2-yl)methyl-6-
      phenyl-2-phenylmethyl-hexanamide; has a control of the second
       (2R, 4S, 5S, 1'S) -5-(4-picolinyloxy) amino-4-hydroxy-N-(1'-
```

35 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-

"न के राजन वेद्यार <mark>प्रश्न</mark>द्धार प्राप्तिन कर्षा कर्षा । विद्यार कर द्वारत है है है है है जो कर प्राप्त द्वार है

hexanamide; with which will be with most;

or It the green's done on the

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· 美多尔斯 鐵矿 1667 克隆
        (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
       isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-
          trifluorobut-1-yl) hexanamide ; was lostly in highesty
       (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
          isopropyl-1'-(4-((1RS)-1-hydroxyethyl)-imidazol-2-yl)]methyl-
          6-phenyl-2-phenylmethyl-hexanamide; *xxxii-iydinali; ddi
        (2R, 4S; 5S, 1'S) = 5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-(1-
         methyl)propyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-
         phenylmethyl-hexanamide; and the fixed on the Strike of the
 10 (2R, 4S, 5S, 1'S)-5-(propylaminocarbonyl) amino-4-hydroxy-N-[1'-
         isopropyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-
         hexanamide;
                                                                   specificathyl-hexal called
          (2R, 4S, 5S, 1'S)-5-(4-hydroxybutanoyl)amino-4-hydroxy-N-(1'-
       _isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-tuchensk.
         phenylmethylhexanamide;
                                                          The the tree of the state of th
        (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(benzyloxy-
        carbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-
                                                               produced secretarions from the
         yl) methyl-hexanamide;
         (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-acetylvalyl)-
         amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-yl)methyl- 68
                                                  the design of the state of the state of the state of
         hexanamide;
        (2R, 4S, 5S, 1'S)-5-[(imidazol-2-yl)methyloxycarbonyl]amino-4-
        hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
                                                                   the first text of the destroyment of
25 (2R, 4S, 5S, 1'S, 1"RS) -5-((1"-(imidazol-2-yl)-2"-methyl) - c:
        propyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
         imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
      isopropyl-1'-(4-(imidazol-2-yl)imidazol-2-yl)]methyl-6-
        phenyl-2-phenylmethyl-hexanamide; 100 typesig-200 grassiq 08
         (2R, 4S, 5S, 1'S) -5- (1-oxo-thian-4-yl) oxycarbonyl) amino-4-
        hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
        phenylmethylhexanamide; a masked to the standard very and the
      (2R, 4S, 5S, 1'S) -5- ((tetrahydrosulfonylpyran-4- (4,44))
35 ...yl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
        yl) methyl-6-phenyl-2-phenylmethylhexanamide; ## https://www.
         (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-(benzyloxycarbonyl-)
        glycyloxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
```

```
imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide
                     - hydrochloride salt; - y 1-1 ha feel- and a same and
                            (2R, 4S, 5S, 1'S)-5-((1, 1-dimethyl-2-glycyloxy) ethoxycarbonyl)-
                   amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
        5 syphenyl-2-phenylmethyl-hexanamidedihydrochloridesalt;
                     1) (2R, 4S, 5S, 1'S) -5- ((1-acetyl) amino-4-hydroxy-N-(1'-isopropyl-
                           1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide;
                           (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
  · : : : : : : : : isopropyl-1!imidazol-2-yl) methyl-6-phenyl-2-(4- :::)
                         benzyloxyphenylmethyl) hexanamide; where the constant
             (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
  isopropyl-1;imidazol-2-yl)methyl-6-phenyl-2-(4-and
             (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-hydroxy-2-
              15 phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-
        to bloomyl]methyl-hexanamide; in the contract of the contract 
             (2R, 4S, 5S, 1'S)-5-((isopropylthiol)carbonyl)-amino-4-hydroxy-
  The Mark w2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'-imidazol-2-
  Taysongoyl]methyl-hexanamide; and avoiding a compact to the compact
                          (2R, 4S, 5S, 1'S) = 5 - [3 - (1H-imidazol-2-yl) - 3 - hydroxy - 4 - yl)
            • * * - methylpentylamido] -4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
  tobesigne y1) methyl-6-phenyl-2-phenylmethyl-hexanamide; Casteria
       -: -vac (2R, 4S, 5S, 1'S)-5-[(4-methoxyphenoxy) carbonyl]amino-4-hydroxy-
                     .. N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
             25 phenylmethyl-hexanamide;
           - '[]-2R,4S,5S,1'S)-5-(t-butylaminocarbonyl)amino-4-hydroxy-N-(1'-
           3-6, isopropyl-1;-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
                         (2R, 4S, 5S, 1'S)-5-(methylaminocarbonyl)-;
              · 11. amino-4-hydroxy-N-(1!-isopropyl-1!-imidazol-2-yl)methyl-6-
   -2-30 graphenylmethyl-hexanamide; the transfer of the transfer of the second se
                         (2R, 4S, 5S, 1'S)-5-phenylaminocarbonyl) amino-4-hydroxy-N-(1'-
-S- (Lygozisopropyl-1!-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
            (2R, 4S, 5S, 1'S)-5-N-(propylaminocarbonyl) amino-4-hydroxy-N-
                         (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
_c_,(2R, 4S, 5S, 1'S)-5-(n-propylaminothiono)amino-4-hydroxy-N-
                         (1'isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
```

```
2R, 4S, 5S, 1'S) -5- (isopropylaminocarbonyl) -amino-4-hydroxy-N-
                   (1'-isopropyl-1'-imidazol-2-yl)methŷl-6-phenylmethŷl-
-(fyror of hexamide; (1, 1-1) -(1, 1-1) hexamide; (1, 1, 2) hexamide;
   (2R, 4S, 5S, 1'S) -5- (aminocarbonyl) amino-4-hydroxy-N-(1'-
            5 isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexamide;
(2R, 4S, 5S, 1'S) -5- (6-quinolinylmethyloxy-carbonyl) amino-4-
                  hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
        phenylmethyl-hexanamide; 15 350 1-13-2-(2016 2013)
                  (2R, 4S, 5S, 1'S) -5- (benzoyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
                  imidazol-2-yl)methyl-6-phenylmethyl-hexanamide: 2004 01
         10
           :- (2R, 4S, 5S, 1'S) -5-(2-furylcarbonyl) amino-4-hydroxy-N-(1'-
                  isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
                  (2R, 4S, 5S, 1'S) -5- (4-methoxybenzoyl) amino-4-hydroxy-N- (1'-
                  isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                  (2R, 4S, 5S, 1'S)-5-benzylcarbonyl) amino-4-hydroxy-N-(1'-1)
         15
                  isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
                  (2R, 4S, 5S, 1'S) -5-(4-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
                 isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                  (2R, 4S, 5S, 1'S)-5-(cinnamoyl) amino-4-hydroxy-N-(1'-isopropyl-
                 1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
         20
                  (2R, 4S, 5S, 1'S) -5- (2-hydroxybenzoyl) amino-4-hydroxy-N- (1'-
                 isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
                 (2R, 4S, 5S, 1'S)-5-(imidazoyl-4-yl-acetyl) amino-4-hydroxy-N-
                 (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
                                                                        to the name of the distance question
                 hexanamide;
                 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
             isopropyl-1'-(4-carbomethoxyethylimidazol-2-yl)]methyl-6-
                 phenyl-2-phenylmethyl-hexanamide; (2014, 2014)
             (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
                 isopropyl-1'-(4-carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-
            phenylmethyl-hexanamide; the state of the st
                (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-
                thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
                yl))methyl-hexanamide; the of the intercognishing is
                (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl) -2-
                thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
             of yl)) methyl-hexanamide; (40 % de an a cold-logo agos (3) .
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13) -- -- (2R, 4S, 5S, 1, S) -2-phenylmethyl-4-hydroxy-5-(5-propyl-2-
               -inthiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
                                            yl))methyl-hexanamide; and
                   .... (2R, 4S, 5S, 1'S) -5- (nicotinyl) amino-4-hydroxy-N-(1'-isopropyl-
              -3-5, (1'-imidazol-2-yl) methyl-6-phenylmethyl-hexamide.
                                                                   Another group of preferred representative compounds are:
         with the (2R, 4S, 5S, 1'S) -5-[di (hydroxymethyl)-methoxycarbonyl] amino-4-
 - Lynedy hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-
                                           phenylmethyl-hexanamide; grade and the property of the propert
              -110 (2R, 4S, 5S, 1'S) -5- (1, 1-dimethyl-2-acetoxyethoxycarbonyl) amino-
                                           4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
                                          phenylmethyl-hexanamide; ball (16) and ten open control of the con
          -P- og by (2R, 4S, 5S, 1'S) -5-((1, 1-dimethyl-2-hydroxy)ethoxy-
         -Solin carbonyl) amino-4-hydroxy-N-(1.'-isopropyl-1'-(4-)
                                          isopropylcarbonyl-imidazol-2-yl))methyl-6-phenyl-2-
    : is to be phenylmethyl-hexanamide dihydrochloride salt;
                                 :0(2R, 4S, 5S, 1'S) -5-((1S)-1-methyl-2-hydroxyethoxycarbonyl)-
                      Y amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
         phenyl-2-phenylmethylhexanamide; went a second and the second and 
          120 (2R, 4S, 5S, 1'S) -5-((1R)-1-methyl-2-hydroxyethoxycarbonyl)-
             -A . (amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
                  phenyl-2-phenylmethylhexanamide;
      ... (2R, 4S, 5S, 1'S) 5-(1-hydroxymethyl-cyclopentyloxycarbonyl)-
                                      amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
    read 25% iphenyl-2-phenylmethyl-hexamide; no see the recommendation
                       .m. od (2R, 4S, 5S, 1h.S) -5- (1, 1-dimethyl-2-hydroxyethoxycarbonyl) amino-
    edition of hydroxy-N-(1!-isopropyl-1!-imidazol-2-yl)methyl-6-phenyl-2-
      West phenylmethyl-hexanamide hydrochloride; was west or
         ر المراجعة (2R, 4S, 5S, 1<sup>N</sup>S) -5- (hydroxyethoxycarbonyl) amino-4-hydroxy-N-
 figure 30 % (1'-isopropyl-1/-imidazol-2-yl) methyl-6-phenyl-2-
                                      phenylmethylhexanamide; and
etc for gg. E(2R,4S,5S,1,S)-5-(2-hydroxy-1-methylethoxycarbonyl) amino-4-
The Property is a second by the second of th
         and a phenylmethylhexanamide done not construct the rest of the second
                                           .: Via More preferred representative compounds are:
                                       (2R, 4S, 5S, 1; S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
       no imagino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-
        ref wigos hexanamides hydrochloride; whose the same fair of the same
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(2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethylhexanamide;
(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl) methyl-6phenyl-2-phenylmethyl-hexanamide; [100ylf-1sd-tonk]
(2R, 4S, 5S, 1'S) -5-(1, 1-dimethyl-2-hydroxyethoxycarbonyl) amino4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-

phenylmethyl-hexanamide hydrochloride; -1/dismity and 10 V (2R,4S,5S,1'S)-5-(hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-i->
phenylmethylhexanamide; and imministrative said (2R,4S,5S,1'S)-5-(2-hydroxy-1-methylethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

phenylmethylhexanamide. The term "alkyl" refers to a straightfor branched chain alkyl radical of the indicated number of carbon atoms.

"C1-4alkyl" as applied herein is meant to include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl; "C1-6alkyl" includes additionally pentyl, isopentyl, 2-methylbutyl, 1-methylbutyl, 2-ethylpropyl, neopentyl, n-

hexyl 2,2-dimethylbutyl, 2-methylpentyl/ and the like.
"Alkoxy" refers to an alkyl group of the indicated number of carbon atoms attached through a bridging oxygen atom.

"Alkylthio" refers to an alkyl group of the indicated number of carbon atoms attached through a bridging sulfur atom.

The term "substituted alkyl" as used herein is meant to include C1-6alkyl, Ar-C1-6alkyl, Het-C1-6alkyl, C3-6cycloalkyl-C1-6alkyl, Ar-C2-6alkenyl, Het-C2-6 alkenyl, C3-6cycloalkyl-C1-6alkyl,

30 C3-6cycloalkenyl-C1-6alkyl or C1-6alkyl substituted with acyl or hydroxyl.

"Alkenyl" refers to a straight or branched hydrocarbon chain of the indicated number of carbon atoms, which contains one or more carbon-carbon double bonds at any stable point

along the chain, such as ethenyl, propenyl; butenyl, propenyl; butenyl, propenyl; and the like.

"Alkynyl" refers to a straight or branched hydrocarbon chain of the indicated number of carbon atoms which contains

```
. The gradual carbon-carbon triple bond at any stable point along the
  This is to chain, such as ethynyl, 2-propynyl, 2-butynyl, 4-pentynyl,
  fig. as as 2-methyl-3-propynyl, hexynyl and the like. 345
The term "acyl" means R12-CO, wherein R12 is H,
            5 C<sub>1-6</sub>alkyl, Ar-C<sub>1-6</sub>alkyl, Het-C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl,
   Ar-C2-6alkenyl, Het-C2-6alkenyl, C3-6cycloalkyl- C1-6alkyl,
 C5-6cycloalkenyl-C1-6alkyl, OH, NHR13, wherein R13 is H,
    Ar-C1-6alkyl, Ar-C1-6alkyl, Het-C1-6alkyl, C2-6alkenyl,
     Ar-C2-6alkenyl, Het-C2-6alkenyl, C3-6cycloakyl-C1-6alkyl, or
  . 10:1 C3-6cycloalkyl, or C5-6cycloalkenyl-C1-6alkyl; or an α-amino
          acid or an α-amino alcohol bonded at the nitrogen.
sinyone ise a "Cycloalkyl" refers to a saturated ring group of the
                 indicated number of carbon atoms. "C3-7cycloalkyl" includes
    * file : cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and
         15 'cycloheptyl.' "Cycloalkenyl" refers to a saturated ring group
                 of the indicated number of carbon atoms, having at least one
            endocyclic carbon-carbon double bond. "C5-7cycloalkenyl"
       includes cyclopentenyl, cyclohexenyl and cycloheptenyl.
           "Aryl", abbreviated as Ar, refers to phenyl or naphthyl,
                optionally substituted with one to three halo, OH, OR10,
    C1-6alkyl, C1-6alkoxy, C1-6alkylthio, C1-6alkylamino, CF3,
ACCORAGE Amino, NO2, carboxy, C1-4alkylcarbonyl, aminocarbonyl,
 The Confidence of the Confiden
                phenyl, C1-6alkyl-, C1-6alkoxy-, HetC1-6alkyl-, HetC1-6alkoxy-,
25 phenylC1-6alkyl-, phenylC1-6alkoxy- or phenyloxy.
As used herein except where noted, the term
     "heterocycle", abbreviated as "Het", represents a stable 5-
second in to 7-membered monocyclic or a stable 7- to 10-membered
   bicyclic heterocyclic ring, which is either saturated or
1 0030 unsaturated, and which consists of carbon atoms and from one
                to three heteroatoms selected from the group consisting of N,
              O and S, and wherein the nitrogen and sulfur heteroatoms may
         ivad optionally be oxidized, and the nitrogen heteroatom may
        int optionally be quaternized, and including any bicyclic group
        35.: in which any of the above-defined heterocyclic rings is fused
          - to a benzene ring. The heterocyclic ring may be attached at
        Dust any heteroatom or carbon atom which results in the creation
               of a stable structure, and may optionally be substituted with
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one to three halo, OH, alkyl, alkoxy, alkyl-Het, alkoxy-Het, alkyl-phenyl, alkoxy-phenyl. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Heteroaryl refers to a heterocycle which has aromatic character (eg., characterized by delocalized electron resonance and the ability to sustain a ring current). Pyridine, imidazole, thiazole, furan and

"Amino acid" means the D- or L- isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine or trifluoroalanine.

In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in Eur. J. Biochem., 158, 9 (1984). Usually lipophilic amino acids are preferred for the moiety B, for instance, Val, Ala, Leu and Ile. It will be understood that, a linkage B-O refers to an oxygen atom bonded to the carboxyl group of an amino acid, and that a B-N linkage indicates a nitrogen atom bonded to the carboxyl group of an amino acid, as; in an amide bond.

"Amino alcohol" refers to an amino acid in which the carboxyl group has been reduced to a methylene hydroxy group.

oxazole are examples of heteroaryl rings. fart and the

Certain chemical names are abbreviated herein for the sake of convenience. Boc refers to the t-butoxycarbonyl radical. Cbz refers to the carbobenzyloxy radical. Bzl refers to the benyzl radical. Ac refers to acetyl. Pharefers to phenyl. BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate. DCC refers to dicyclohexylcarbodiimide. DMAP refers to

dimethylamin-opyridine. DMSO refers to dimethylsulfoxide. HOBT refers to 1-hydroxybenzotriazole. NMM is N-methylmorpholine. DTT is dithiothreitol. EDTA is ethylenediamine tetraacetic acid. DIEA is diisopropyl

ethylamine. DBU is 1.8 diazobicyclo[5.4.0]undec-7-ene. DMSO is dimethylsulfoxide. DMF is dimethyl formamide; Lawesson's reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide and THF is tetrahydrofuran. HF refers to hydrofluoric acid and TFA refers to trifluoroacetic acid.

The compounds of formula (I):

wherein R<sup>4</sup> is CO-NR CHR<sup>6</sup>R<sup>7</sup>, R<sup>5</sup> is R<sup>10</sup>R<sup>11</sup>N-, and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>6</sup> are as defined in formula (I), are prepared by:

with a compound of formula (III):

ad alle solden you ashage will me HR'N-CHR6'R7!

where R1', R2', R3', R5', R6' and R7' are as defined for

formula (I) with any reactive groups protected, Prl is H or a hydroxyl protecting group, and L' is OH or a leaving group;

or Lyouned and paragraphy (i) coupling a compound of the formula (IV):

with a compound of the formula (V):

UL

HOE'S reise to 1- 16(V) space we we we we

wherein A' and B' are as defined in formula (I) with any reactive groups protected; or seems benefited:

(c) coupling a compound of the formula (VI)

with a compound of the formula (VII) : 200 000 3862 ...

10

A'-L'

(VII)

and,

- 2) if appropriate, a coupling agent; and
- 3) removing any protecting groups and
- 5 4) forming a pharmaceutically acceptable salt thereof.

The coupling reactions may be accomplished by activating the substrate with a reactive functional group in situ or prior to the coupling reaction, such that it is reactive with an amino group. For instance, acids may be converted to acid chlorides, bromides, activated esters or anhydrides, or by adding a coupling reagent. Coupling agents are well known in the art for activating a functional group in situ,.

Exemplary of such agents are DCC and other carbodismides,

DMAPEC, BOP and PPA. These coupling agents may optionally be used with other reagents, such a HOBT, NMM and DMAP, which may facilitate the reaction.

Suitable leaving groups, L', are those which are displaceable by an amino group, such as bromo, chloro, a substituted acyl (eg. trifluoroacetyl, bromobenzoyl, nitrobenzoyl) or a substituted phenol (eg. 4-nitrophenol) and the like. If L' is OH, so that A-OH is an acid, it will be appropriate to use a coupling agent as hereinbefore described.

For instance:

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yellowagery When A is a substituted alkyl group, such as a substituted alkyl group, such as

When A is R<sup>17</sup> (R<sup>18</sup>R<sup>19</sup>C)<sub>m</sub>-W, Ar-W or Het-W, and W is C=O, 5 a A-L' may be at carboxylic acid halide, activated ester or adanhydride, or a carboxylic acid in the presence of a coupling agent. Methods for preparing such compounds are well known.

(Accepted When W is OC=O, A-L' may be a chloro- or bromo-formate,

i or an activated carbonate. Haloformates may be prepared by

10 clreacting the appropriate alcohol with phosgene or carbonyldibromide. CARCTIVATED carbonates may be prepared by the propriate alcohol with a suitable carbonate such as bis (4-nitrophenyl) carbonate.

and the percent When Wais a SO2 par A-L' may be a sulfonyl halide; which may

15 to be prepared from the corresponding sulfonic acid.

When Wis SC=0, A-L may be a halothioformate, which may be prepared from a carbonyldihalide and an appropriate mercaptan.

When W is PO(OR<sup>22</sup>), A-L' may be a phosphonyl halide,

20 which may be prepared from the corresponding phosphonic acid.

Compounds wherein A is R<sup>17</sup>(R<sup>18</sup>R<sup>19</sup>C)<sub>m</sub>-W, Ar-W or Het-W,

and W is NR'C=O are ureas, and may be prepared by reacting a

compound of formula (VII) with an isocyanate of the formula

R<sup>17</sup>(R<sup>18</sup>R<sup>19</sup>C)<sub>m</sub>-NCO, Ar-NCO or Het-NCO, in a suitable solvent

25 such as methylene chloride, optionally with heating.

Compounds of formula (III), wherein X is nitrogen, are imidazoles and may be prepared according to Scheme 1, wherein Pr<sup>2</sup> is a removeable amino protecting group, and R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> correspond to R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> as defined for formula (I), or a group which may be converted into R<sup>7</sup>, R<sup>8</sup> or R<sup>9</sup>, with any reactive groups protected.

Scheme 1

The amino aldehydes are generally known or are prepared by methods well known in the art, for instance, by reduction of a suitable α-amino acid ester with diisobutylaluminum hydride. Further reaction of the aldehyde with a gem 5 dialdehyde, or diketone, and ammonia yields the desired mail inidazole. Alkylation and further modification of the substituent groups of the imidazole are within the skill of the art. Such a method and other methods for preparing imidazoles are disclosed, for instance, by Baldwin et al., J. 10 Med. Chem., 29, 1065 (1986), Angeway Cheman Int., 22, 560 1 (1983); and Hughey et al., Synthesis, 1489d(1980) . 180 Alternately, acyl imidazoles may be prepared by coupling an α-amino acid to a substituted 4-amino-isoxazole, and subsequent reduction and base catalyzed rearrangement as disclosed generally by Reiter, L.A., J. Org. Chem., 52, 2714 (1987). Intermediate compounds of formula (VIII) are a part of this invention. Preferably, R7, is C1-6alkyl and more preferably C3-6alkyl. Suitably, R8' and R9' are H, NO2, Br, COR<sup>12</sup>, CF<sub>3</sub>, Ar, C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl-R<sup>15</sup>, wherein R<sup>12</sup> is H,

hydroxyl group. Preferably R<sup>9</sup> is H or COR<sup>12</sup>. ACC.

Compounds of formula (III), wherein X is sulfur, are
thiazoles and may be prepared according to Scheme; 2, wherein
L' is a suitable displaceable group.

10.5 20 C1-6alkyl, Ar, OC1-6alkyl, NH2, and R15 is OH or a protected

25

#### Scheme 2 to single wall

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Accordingly, a thioamide is reacted with a ketone or aldehyde. Thioamides are commonly prepared from carboxamides by reacting the corresponding carboxamides with a reagent such as Lawessons reagent, as disclosed, for instance, by Hamada et al., Tet. Lett., 931 (1991). Suitable displaceable groups are those which are displaced by a sulfur nucleophile,

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such as chloride, bromide, iodide, mesylate, p-tolunesufonate groups, and the like.

Compounds of formula (III), wherein X is oxygen, are oxazoles and may be prepared according to Scheme 3 from common amino acids.

Carried State of Stat

#### Scheme 3

Typically the acid may be coupled to an appropriately substituted amino alcohol by common techniques, as described above, and cyclized by treatment with thionyl chloride to yield an oxazoline, as described by Meyers et al., J. Org. Chem., 43, 1372 (1978). Oxidation of the oxazoline, such as described by Evans et al., J. Org. Chem., 44, 497 (1979), yields an oxazole.

The compounds of formula (II), (IV) and (VI), wherein R<sup>2</sup> is H, are prepared, for instance, according to Scheme 4.

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### Scheme 4

Other methods for preparing protected 5-amino-4-hydroxy2,5-disubstituted-pentanoate esters and acids, and the corresponding Y-lactones, are well known and are disclosed, for instance, in Szelke et al., U.S. Patent 4,713,455, Boger et al., U.S. Patent 4,661,473, EP-A 0 352 000, Evans et al., J. Org. Chem., 50, 4615 (1985), Kempf, J. Org. Chem., 51, 3921 (1986), Fray et al., J. Org. Chem., 51, 4828 (1986), Halladay et al., Tett. Lett., 24, 4401 (1983), Wuts et al., J. Org. Chem., 53, 4503 (1988), DeCamp et al., Tett. Lett., 32,1867 (1991), and Szelke et al., WO 84/03044, all of which are incorporated herein by reference.

15 The compounds of formula (II), (IV) and (VI), wherein R<sup>2</sup> is OH, are also prepared by methods common in the art such as those disclosed in U.S. Patent 4,864,017, and Thaisrivongs et al., J. Med. Chem., 30, 976 (1987).

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Compounds of formula (I), wherein  $\mathbb{R}^5$  is  $\mathbb{R}^6-\mathbb{N}\mathbb{R}^{11}$ , are prepared according to Scheme 5, Scheme 6 or Scheme 7:

### Scheme 5

$$H_2N$$
 $OP_1^1$ 
 $R^3$ 
 $R^4$ 
 $R^5$ 
 $R^5$ 
 $R^5$ 
 $R^5$ 
 $R^5$ 
 $R^7$ 
 $R^8$ 
 $R^8$ 
 $R^8$ 
 $R^8$ 
 $R^8$ 
 $R^8$ 
 $R^8$ 
 $R^8$ 
 $R^8$ 

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#### Scheme 7

wherein R1'-R4', R7' and R8' are as defined in formula (I)

with any reactive groups protected, L' is a leaving group,

15' such as halogen, and Pr1' is a hydroxy-protecting group

in a gradient and a second as halogen, and Pr1' is a hydroxy-protecting group

Compounds wherein  $R^4$  is  $R^6NR^{11}$  are prepared in an analogous manner from a compound of formula (IX):

Suitable protecting groups for the amino, hydroxyl, carboxylic acid, mercaptan group, and reagents for deprotecting these functional groups are disclosed in Greene et al., PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Second Edition, John Wiley and Sons, New York, 1991. Deprotection indicates the removal of the protecting group and replacement with an hydrogen atom. In particular, suitably substituted acetyl, benzyl and silyl groups are useful for protecting the hydroxyl group. The acetyl group is commonly removed by reacting the compound with a base, such as an alkali metal hydroxide, in a mixture of an alcohol and water. The silyl group, such as trimethyl silyl, dimethyl-t-butyl silyl, and t-butyl-diphenyl silyl may be removed by a fluoride reagent, such as a tetra-alkyl ammonium fluoride, or by acid hydrolysis. The benzyl group may be removed by catalytic hydrogenation.

Suitable protecting groups for the amino group are those disclosed by Greene et al., as indicated previously. The benzyloxycarbonyl and t-butoxycarbonyl groups are especially useful amino protecting groups.

The present invention includes pharmaceutically acceptable acid addition salts. Acid addition salts of the present compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, maleic, succinic or methanesulfonic. The acetate salt form is especially useful. If the final compound contains an acidic group, cationic salts may be prepared. Typically the parent compound is treated with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation. Cations such

cas Na+, K+, Ca++ and NH4+ are examples of cations present in pharmaceutically acceptable salts. Certain of the compounds Girlin. I form inner salts or zwitterions which may also be acceptable. and of mothercompounds of the present invention selectively bind 55 to retroviral proteases in the same manner as the virally "coded natural substrates of the proteases and compete with these substrates for protease, thereby serving to inhibit viral replication by blocking the formation of crucial viral proteins from polyprotein precursors by the protease, and 10 hence, to inhibit disease progression in vivo. The present compounds achieve such beneficial therapeutic effect because they contain unique structural features which impart Vidential desirable pharmacokinetic properties to the compounds. One such property is long duration of action. We have found that 15 substitution of a heterocycle, especially imidazole, in the putative P21 position of the present compounds affords compounds which retain good enzyme binding affinity, good antiviral activity, a favorable duration of action and water solubility for good drug delivery. 20 When a compound of the present invention is administered to an animal infected or potentially infected with a retrovirus, viral replication is inhibited and hence disease progression is retarded. Inasmuch as the amino acid 180 sequences of the protease binding and peptide bond cleavage sites of various retroviruses appear to be highly conserved, an inhibitor is likely to be broadly active against more than one retrovirus. Also, DNA viruses which are dependant upon "" virally encoded proteases, such as the hepatitis virus, may also be susceptible to such treatment. The contribution The compounds of formula (I) are used to inhibit retroviral replication, and are useful in treating mammals, particularly human patients, who are infected with susceptible retroviruses and require such treatment. The method of treating a retroviral disease in a mammal, particularly a human, comprises internally administering (e.g. orally, parenterally, buccally, trans-dermally, leads rectally or by insufflation) to said mammal an effective

amount of a compound of formula (I), preferably dispersed in

a pharmaceutical carrier. Dosage units of the active ingredient may be selected by procedures routine to one skilled in the art, and are generally in the range of 0.01-50 mg/kg. These dosage units may be administered one to ten times daily for acute or chronic infection we Preferably the compound is administered at a level of 1-10 mg/kg, two to four times daily. No unacceptable toxicological effects are indicated when compounds of this invention are administered in the above noted dosage range.

The present invention also provides a method of treating disease states associated with HIV infection or Acquired Immune Deficiency Syndrome (AIDS), comprising administering an effective amount of a compound of formula (I), preferably dispersed in a pharmaceutical carrier.

Beneficial effects may be realized, by co-administering, individually or in combination, other anti-viral agents with the protease inhibiting compounds of the present invention.

Examples of anti-viral agents include nucleoside analogues, phosphonoformate, rifabutin, ribaviran, phosphonothicate oligodeoxynucleotides, castanospermine, dextran sulfate, alpha interferon and ampligen. Nucleoside analogues, which include 2',3'-dideoxycytidine(ddC), 2',3'-dideoxyadenine(ddA) and 3'-azido-2',3'-dideoxythymide (AZT), are especially useful. AZT is a preferred agent. Suitably, pharmaceutical compositions comprise an anti-viral agent, a protease inhibiting compound of the present invention, and a pharmaceutically acceptable carrier.

This invention is also a pharmaceutical formulation which comprises a compound of formula (I) and a pharmaceutically acceptable carrier. Pharmaceutical acceptable carrier are well known in the art and are disclosed, for instance, in SPROWL'S AMERICAN PHARMACY, Dittert, L. (ed.), J.B. Lippincott Co., Philadelphia, 1974, and REMINGTON'S PHARMACEUTICAL SCIENCES, Gennaro, A. (ed.), Mack Publishing Co., Easton, Pennsylvania, 1985.

Pharmaceutical compositions of the compounds of the present invention, or derivatives thereof, may be formulated as solutions or lyophilized powders for parenteral

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6.37 candministration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable ation carrier prior to use. The liquid formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable 5 diluents are normal isotonic saline solution, standard 5% / 10.40 dextrose in water or buffered sodium or ammonium acetate "Solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or 10 nebulizer for insufflation. It may be desirable to add excipients such as ethanol, polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, 15 tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Liquid carriers include syrup, soy bean oil, peanut oil,

20 Solive oil, glycerin, saline, ethanol, and water.

with an entire solubilizing agents, such as dimethylsulfoxide, ethanol or 31 formamide, may also be added. Carriers, such as oils, optionally with solubilizing excipients, are especially The suitable. Oils include any natural or synthetic non-ionic

25 water-immiscible liquid, or low melting solid, which is

" - capable of dissolving lipophilic compounds. Natural oils, ould to Youch as triglycerides are representative. In fact, another

see siaspect of this invention is a pharmaceutical composition comprising a compound of formula (I) and an oil.

30 30 Sala Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Solubilizing agents, such as dimethylsulfoxide or formamide, may also be added. The carrier may also include a sustained release material

35 besuch as glyceryl monostearate or glyceryl distearate, alone About I for with a wax. The amount of solid carrier varies but, The state preferably, will be between about 20 mg to about 1 g per

dosage unit. The pharmaceutical preparations are made

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following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

A suitable dosage form for oral administration has been prepared by dissolving the peptide of Example 1 (312.5 mg) in dimethyl sulfoxide (1 mL) and diluting to a concentration of 12.5 mg/mL with soybean oil. A suitable dosage form for intravenous administration has been prepared by dissolving the compound of Example 1 (0.02/g) in dimethyl sulfoxide (1 mL) and diluting to 20 mL with a 70% propylene glycol/30% ethanol solution.

For rectal administration, a pulverized powder of the compounds of this invention may be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository. The pulverized powders may also be compounded with an oily preparation, gel, cream or emulsion, buffered or unbuffered, and administered through a transdermal patch.

The pharmacological activity of the compounds of this invention may be demonstrated by enzyme assays to determine the inhibitory activity of the retroviral protease, by in vitro cellular-based assays to determine the ability of the compounds to penetrate cells and inhibit viral replication, and by pharmacokinetic assays to determine oral bioavailability, drug half-life and clearance. These assays are well known in the art.

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### ENZYME ACTIVITY TO THE STEEL THE RESERVE TO BE ASSESSED.

The ability of the compounds of this invention to inhibit the HIV-1, protease enzyme may be demonstrated by using the assay disclosed by Dreyer et al., Proc. Natl. Acad. Sci., U.S.A., 86, 9752 (1989), Grant et al., Biochemistry, 30 8441 (1992), and EP-A 352 000. The Ki for the compounds of

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this invention are in the range of 1 nM to 5 µM. Preferred
      go compounds have Ki's of less than 100 nM.
 boloov) Gp.J., 0-20 smuloy into a still desagger, gase and as for
  O to ginfectivity of kan a blo a set (Cor he was a leaven)
   6.5. choi: The ability of the compounds of this invention to gain
 mess as mentry to cells infected with the human immunodeficiency
    wirus, and to inhibit viral replication in vitro may be
  'da to demonstrated using the assay described by Meek et al.,
 Assat & Nature, 3343,690 (1990), and Petteway et al., Trends
nt blode Pharmacol. Sci, 12, 28; (1991) . The IC50 for the compounds of
    and this invention are in the range of 0.1 to 10 µM.
 they have become and the object of the fattened ample made
   En a cytotoxicity deligning he has both in a se-
 in Religious Cytoitoxicity is assessed by both direct microscopic
        examination of trypan blue stained cells (T-lymphocytes) and
yd fod: by the treated culture stability to metabolize the
    fac stetrazolium@salteXTT- (2,3-bis[2-methoxy-4-nitro-5-tg
sulfophenyl]-2H-tetrazolium-5-carboxanilide; sodium, salt), to
    Los (its formazan, dye ), The XTT assay allows determination of the
        50% toxic concentration of compounds for the cell/virus
and disproved the salar process of that go note his as associate and process
  : not temps so Dual jugular cannulated Sprague Dawley rats weighing 200
        to 250 g were utilized in all studies. All dosing and sample
  .00 92 (collection was done from conscious rats. Before dosing, a
 #01. 16 time: 0: blood: sample,0:300: μL, was: drawn using one of the
        catheters. Utilizing the second catheter the rats were dosed
slovel (intravenously.a At 1,5,10,330, 60, 90,6120, 150, 180 and 210)
5. 4:30 min after dosing, 300 ML blood samples were drawn. To The rats
to make dosedworally were administered the compound by attilizing a 22
  All of gauge gastric gavage needle and samples were drawn sat 30, 60,
c1 - 11: 90/2 120/3240/ 360/ 480/ 600/ 720 and 1440 min. The blood
     samples were placed-in precooled tubes containing 30 mL of
   35g sodium citrate and centrifuged in a microfuge to The plasma
or my was transferred then snap frozen on dry ice, and stored at
 odd de -70°C:until analyzed. His ridnomes feat. de est to bestreen
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Standard stock solutions (1 mg/mL) of inhibitor was prepared in 100% DMSO. A dilution series of the stock solutions were prepared in a total volume of 0.1 mL (pooled normal rat plasma/DMSO) to yield final concentrations of 0 and 0.5-120X the Ki of the inhibitor. All dilutions were performed in triplicate. These spiked plasma solutions were extracted with 0.5 mL acetonitrile by vigorous vortexing, followed by centrifugation for 10 min. An aliquot (0.4 mL) of the supernatant was removed and dried in Eppendorf tubes 10 31 10 Tusing a Speed-vac. The (resulting residue was) redissolved in DMSO. The inhibition of the HIV-leprotease activity was assayed as follows. An aliquot of the extracted sample was: added to a 50 µL mixture containing 1X MENDT buffer, 1 mM substrate and incubated at 37°C < 10 min of The reaction was in 15 then initiated by the addition of HIV-1 protease and continued at .37°C for an additional 15 min, then quenched by the addition of TFA (0.5% final concentration) realnitial car (the rates were determined for each standard curve as the fraction est to not remaining enzymatic activity (vi/vo) at each inhibitor 20 concentration, in which vo is the velocity of the Id 68 (inhibitor concentration)=0 sample. Assuming that all of the original inhibitor in the spiked samples was extracted, the values of vi/vo were plotted versus inhibitor concentration the take of the original extracted sample and fitted to the equation: to the 25 to vi/vo=[AEt - It - Kit+ (Ki-AEt-It) 0.5]/(2AEt), p 08 7 ob at B At in which Et is the total enzyme concentration at time zero, Ki is the apparent inhibition constant and A is the fraction of the terror of tactive enzyme. The one of the total light and the sac Ex vivo animal plasma samples containing unknown levels of protease inhibitor were prepared and analyzed as described for the standard curve described above. The concentration of inhibitor in these samples was then determined using the Ki and A parameters from the fitted standard curve according to the following equation:  $c[I_t=AE_t[1-(v_1//v_0)]+K_1(v_0/v_1)$ . 5 35 35 of The data was plotted as the natural (log (ln) of the 1: looplasma concentration versus time on semilogarithmic paper to generate the plasma concentration-vs-time curves? Using the IV data, the apparent terminal rate constant was determined

form the linear regression analysis of the plasma
concentration-vs-time curve. The elimination half-life
(t1/2) was derived by dividing ln 0.5 (=0.693) by the
terminal rate constant. The area under the plasma

5 concentration-vs-time curve (AUC) was determined by using the ln/log trapezoidal rule. C<sub>max</sub> represents the maximal plasma concentration and t<sub>max</sub>, the time following drug administration at which C<sub>max</sub> was observed. Both values were estimated by inspection of the plasma concentration-vs-time curve. Total plasma clearance (CL) was calculated by

dividing the dose by the AUC. The fraction of the oral dose by the available to the systemic circulation (the bioavailable fraction, F) was determined by the equation: F = [AUCpo/DOSEpo] xx[DOSEiv/AUCiv].

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Hertz.

The Examples which follow serve to illustrate this invention. The Examples are not intended to limit the scope of this invention, but are provided to show how to make and use the compounds of this invention.

201 Centigrade. Mass spectra were performed using fast atom bombardment (FAB) or electro-spray (ES) ionization. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

NMR were recorded at 250 MHz using a Bruker AM 250

(30) Spectrometer, unless otherwise indicated. Chemical shifts
are reported in ppm(δ) downfield from tetramethylsilane.

Multiplicities for NMR spectra are indicated as: s=singlet,
d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of

doublets, dt=doublet of triplets etc. and br indicates a

(80) broad signal. J indicates the NMR coupling constant in

Celite® is filter aid composed of acid washed

inv all diatomaceous silica manufactured by Mansville Corp., Denver,

car 35. Colorado. Florisil® is an activated magnesium silicate

chromatographic support and is a registered trademark of

Floridon Co., Pittsburgh, Pennsylvania. Sat. indicates a

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saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant.

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Preparation of (2R:4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide hydrochloride). Seidergalinims

10 a) (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-

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Cbz-valinal (4.6 g, 1 eq) and glyoxal trimeric dihydrate (1.33 g, leq) were stirred in MeOH at -10°C. Ammonia was bubbled through the solution for several min and the mixture was allowed to stir for 4 h at -10°C. The mixture was allowed to warm to room temperature over 14 h, then was poured into 250 mL water. The suspension was filtered and the filter cake washed twice with water to give the title compound as a white solid (1.9 g, 36%). NMR(CD3OD) δ 7.28

20 (5H, m), 6.89 (2H, s), 5.04 (2H, dd), 4.46 (1H, d), 2.10 (1H, m), 0.91 (3H, d), 0.70 (3H, d); MS(CI/CH<sub>4</sub>), m/e 274.2, [M+H]<sup>+</sup>, 230.1, 166.1, 123.1, 91.1.

Jelesan (1) a w. 31 181 10 100 20 ab 6

- b) (1'S)-1'-amino-1'-isopropyl-1'-(imidazo-2-yl)methane

  (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2yl)methane (1.9 g) was stirred in methanol over 10% Pd/C (200
  mg). Hydrogen was bubbled through the solution for 1 h and
  the solution was maintained under; a positive hydrogen
  atmosphere overnight. The mixture was filtered through
  Celite® and was evaporated to a tacky solid (720 mg; 75%).
  NMR(CDC13) & 6.87 (2H, s), 3.88 (1H, d), 2.04 (1H, m), 0.81
  (6H, dd); MS(DCI/NH3) m/e 190.2 [M+H]+

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butylmethyl) siloxy-5-(t-butoxycarbonyl) amino-6-phenyl-

hexanoic acid (200 mg, 0.38 mmol) in dichloromethane, (1'S)to 1 - 1;-amino-1;-isopropyl-1'-(imidazo-2-yl)methane (48 mg, 0.35 . milit commol), BOP reagent (168 mg, 0.38 mmol), and triethylamine The mixture was stirred (0.053 mL, 0.38 mmol); were added. The mixture was stirred . Manufact secunder, argon overnight, and washed successively with water, 5% Remarks , waqueous, sodium bicarbonate; and saturated aqueous sodium Ou. & & (a chloride. The solution was dried over MgSO4, filtered, and the solid was chromatographed (silica, 4% methanol/dichloromethane) to afford the title compound as a white solid (0.154 g, 68%). NMR(CDCl<sub>3</sub>)  $\delta$  7.18 (10H, m), 6.91 (2H, d), 6.32 (1H, d), 4.69 (1H, d), 4.40 (1H, moon to t), 3.92 (1H, eq), 3.63 (1H, m), 2.84 - 2.31 (6H, m), 1.67 (4H, m), 1.24 (9H, s), 0.89 (9H, s), 0.74 (6H, dd), 0.05 (6H, here is a d); MS(DCI/NH3) m/e 649.6 [M+H]+. ... e to grea 50.5**15** 对抗 抗氯甲酚 **物效应多式 电**分散式

butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(imidazo-2-yl)] methyl-hexanamide hydrochloride

The compound of Example 1(c) (0.140 g) was stirred in

20 THF at room temperature under an argon atmosphere.

Tetrabutyl ammonium fluoride (0.38 mL, 6 eq) was added and the solution was stirred overnight. The mixture was diluted with water and extracted with dichloromethane (3X). The combined organic extracts were washed with water and evaporated. The residue was treated with 1 eq of methanolic evaporated. The residue was treated with diethyl ether and extracted to give the title compound as a white solid (95 mg, 83%). NMR(DMSO-d6) & 7.78 (1H, d), 7.16 (10H, m), 6.71

(2H, s), 6.39 (1H, d), 4.68 (1H, m), 4.52 (1H, d), 2.71 (3H, d), 2.48 (3H, m), 1.97 (1H, m), 1.61 (1H, m), 1.30 (9H, s), 0.78 (3H, d), 0.61 (3H, d); MS(DCI/NH3) m/e 535.4 [M+H]+.

#### m distinguisment in the second of the second

uoi35 Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(tus os beabutoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-(4aminocarbonyl-thiazo-2-yl)]methyl-hexanamide

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a) Boc-valineamide

To a solution of di-t-butyl-dicarbonate (7:15 g, 1 eq) in dry dichloromethane was added valinamide hydrochloride (5.0 g, 1 eq) and triethylamine (9:14 mL, 2 eq). The mixture was heated to reflux for 4 h, and cooled to room temperature. The organic layer was washed twice with water and evaporated to give the title compound (6.03 g, 85%). NMR (CDCl3) δ 6.00 (1H, br), 5.54 (1H, br), 5.01 (1H, br), 3.93 (1H; dd), 2.12 (1H, m), 1.44 (9H, s), 0.92 (6H, dd).

(a. b) Boc-valinethioamide (i.e., (ii., a.e.) 16.3 (ar (art))

Boc-valineamide (0.5 g) was stirred in dry THF at room temperature under argon. Lawesson's reagent (1.56 g, 0.6 eq) was added and the mixture was stirred overnight. The solvent was evaporated and the residue chromatographed (silica, 2.5% methanol/dichloromethane) to give the title compound as a white solid (0.373 g, 70%). NMR(CDCl3) & 8.59 (1H, br s), 8.09 (1H, br s), 5.41 (1H, d (br)), 4.20 (1H, dd), 1.99 (1H, m), 1.39 (9H, s), 0.90 (6H, m).

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entire in the carboethoxythiazo-2-yl) methane is the carboethoxythiazo-2-yl) methane

Boc-valinethioamide (0.265 g) was stirred in dry acetone under argon at -10°C. Ethylbromopyruvate (0.16 mL, 1.1 eq) 25 was added and stirred for 1 h at -10°C. The solution was poured into a well-stirred mixture of chloroform and water and then saturated with sodium bicarbonate. The organic phase was separated and the aqueous layer extracted with chloroform. The combined organic extracts were dried over 30 MgSO4, filtered, and evaporated to an oil; The oily residue was treated with trifluoroacetic anhydride (0.16 g) and pyridine (0.2 g) in dichloromethane for 1 h at -20°C. Excess solvent was removed in vacuo and the residue dissolved in dichloromethane. The solution was washed with sat. aqueous 35 sodium bicarbonate and 1.0N KHSO4 until pH 7.0 The solution was dried over sodium sulfate, filtered, and evaporated to an oil which was chromatographed (silica, 4% methanol/ dichloromethane) to give the title compound as a tan solid.

1.53 .5. 25 NMR(CDCl<sub>3</sub>): δ 8.04 (1H; as), 5.26 (1H; abrid), 4.85 (1H, m), 2 swip 4:37 (2H, rq); 2.40 (1H, m), 1.41 (9H; s), 1.34 (3H, t), 0.93 (3H, d); 0.84 (3H, d). (3H, d). (3H, d). (3H, d).

5 d) (1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'-(4-

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ALC: 855 (m. A.) 68.8 (m. 101, Ed., 100, Ed., 100, Ed., 100

The compound of Example 2(c) (50 mg) was stirred in THF

at 0°C. Excess 1.0N NaOH was added and the mixture was

stirred for 12 h at 0°C. The mixture was diluted with 1.0N

10 citric acid and extracted with dichloromethane (3X). The

combined organic extracts were evaporated and dried in vacuo

to give the title compound (0.045 g, 98%). NMR(CDCl3) & 8.08

(1H, s), 5.19 (1H, m), 4.80 (1H, m), 2.31 (1H, m), 1.38 (9H, s), 0.86 (6H, dd).

e) (1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'(4-aminocarbonylthiazo-2-yl)methane

carboxythiazo-2-yl)methane (0.078 g, 0.26 mmol) was stirred

under argon in dry THF at -40°C. NMM (0.06 mL; 0.55 mM) and
isobutyl chloroformate (0.034 mL; 0.26 mmol) were added.

After stirring 15 min, ammonia was bubbled through the

mixture for several min. The solution was warmed to room

termperature and the THF evaporated. The residue was diluted

termperature and the THF evaporated. The residue was diluted

with ethyl acetate and washed successively with 1.0N citric

several acid, 5% aqueous sodium bicarbonate, and sat. aqueous sodium

new rechloride. The organic layer was dried over MgSO4, filtered,

be satisfied and evaporated to a solid which was chromatographed (silica,
be of 3% methanol/dichloromethane) to give the title compound as a

30 white solid (0.052 g, 67%). NMR(CDCl3) & 8.02 (1H, s), 7.14

(1H, ms(br), 6.28 (1H, s(br)), 5.24 (1H, d(br)), 4.82 (1H, m),

(101 c. (2.30 (1H, m), 1.39 (9H, s), 0.92 (6H, dd).

(2R, 4S, 5S, 1'S) -2-phenylmethyl-4-(t-butyldimethylsiloxy) -5-35-(t-butoxy carbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(4-aminocarbonyl-thiazo-2-yl)] methyl-hexanamide

The compound of Example 2(e) (52 mg) was stirred in neat trifluoroacetic acid for 10 min and evaporated. The residue

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was diluted with methanol and treated with 2 eq of conc. HCl. The solvents were evaporated and dried (in vacuo; to give a white solid. This solid (40 mg) was added to a solution of (2R, 4S, 5S) -2-phenylmethyl-4-(t-butyldimethyl) siloxy-5-(tbutoxycarbonyl)amino-6-phenyl-hexanoic acida (97 mg, 1.1 eq), DCC (38 mg, 1.1 eq), and HOBT (0.05 gr. 2.2 eq), in DMF at room The name temperature under argon. N-methylmorpholine (0.04 mL; 2.2 eq) was added and the mixture; was stirred overnight. mixture was filtered through Celite®, evaporated, and diluted 10 with ethyl acetate. The solution was washed successively with 1.0N citric acid, 5% aqueous sodium bicarbonate, and (1) and sat. aqueous sodium chloride of The organic layer was to the chromatographed (silica, 2.5% methanol/dichloromethane) to yield the title compound (60 mg, 55%). NMR(CDCl3)  $\delta$  7.89 (1H, s), 7.60 (1H, d), 7.24 (10H, m), 6.82 (1H, m), 5.12 (1H, m), 4.89 (1H, m), 3.92 (1H, q), 3.81 (1H, dd), 2.73 (4H, m), 2.21 (1H, m), 1.73 (2H, m), 1.40 (9H, s), 1.23 (1H, m), 0.93 (9H, s), 0.84 (6H, dd), 0.11 (6H, d), (2+1)

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g) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-) Sec. ( 20 ) butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(4aminocarbonyl (thiazo-2-yl) ]methyl-hexanamide

The compound of Example 2(f) (60, mg) was stirred in dry Fifth the THF under argon and tetrabutylammonium fluoride (0.50 mL, 6 eq) was added. The solution was stirred at room temperature overnight. After diluting with water, the aqueous layer was million in About the extracted with dichloromethane! (3X) = 6The combined organic extracts were washed with water, evaporated, and triturated with diethyl ether and ethyl acetate to give a tan solid. The solid was chromatographed (silica gel, 4% 11 ; 98 methanol/dichloromethane) to give the title compound as a white solid (0.022 g). NMR(CDCl<sub>3</sub>)  $\delta$  7.90 (1H, s), 7.15 (10H, m), 6.39 (1H, d), 5.93 (1H, br s), 5.06 (1H, dd), 4.91 (1H, d), 3.90 (1H, d), 3.67 (2H, m), 2.91 (4H, m), 2.64 (1H, d), 2.13(1H, m), 1.87 (3H, m), 1.36 (9H, s), 0.83 (6H, dd);  $MS(DCI/NH_3)$  m/e 612 [M+NH<sub>4</sub>]<sup>+</sup>, 595 [M+H]<sup>+</sup>, 495, 413.1, 391, 374, 356, 239.1, 202, 185.

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monoid micros to the Lycongonia threatment Example 3
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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(tbutoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-(thiazo-2yl)lmethyl-hexanamide

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it = 1'a): (1'S)-1'-(t-butoxycarbonyl)amino-1'-isopropyl-1'-(thiazoia t == 2-yl)methane singama share of second share the

The compound of Example 2(c) was stirred in neat quinoline. Cu.powder (0.50 g) was added and the suspension was heated to 160°C for 2 h. After cooling to room

house of temperature, the solution was diluted with ethyl acetate and the suspension was heated to 160°C for 2 h. After cooling to room

house of temperature, the solution was diluted with ethyl acetate and the suspension to the solution was diluted with ethyl acetate and the suspension to the suspension of the suspens

15 idark oil in The oil was chromatographed (silica, 4% in bounding methanol/dichloromethane) to give the title compound as an accordance oil NAN NMR (CDCl<sub>3</sub>) (δ.7.68 (1H, d), 7.19 (1H, d), 5.26 (1H, d), 4.88 (1H, m), 2.31 (1H, m), 1.43 (9H, s), 0.92 (3H, M), 0.84 (3H, d).

20 (31) (31) (31) (40) (40) (40) (40) (40)

b) (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t
-nedsea(butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-(thiazo-2
nedsea(butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'-(thiazo-2-

(as 0.00) (D. Defollowing the procedure of Example 2(f)-2(g), except of 25 of using the compound of Example 3(a) in place of (1's)-1'-(t-1'c) butoxycarbonyl) amino-1'-isopropyl-1'-(4-aminocarbonylthiazo-deuc2-yl) methane, the title compound was prepared (88%).

1 NMR (DMSO-d6) & 8,31, (1H, d), 7.62, (1H, d), 7.49 (1H, d), 7.16

-8% ((10H, m), 2.61 (6H, m), 1.28 (9H, s), 0.89 (3H, dd); 30 MS(DCI/NH3) m/e3552.3 [M+H]<sup>+</sup>, 413.2, 331.1, 183.1, 157.1, 142.0, 120.13 S. Ost A. (288.2)

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-light 2-yl) 1 methyl-hexanamide (-a) - forward factor of the cold method as bound to the state of the cold method for the cold of the cold for a state of the cold factor of the cold for the cold for the cold factor of the

a) (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(benzimidazo-2-yl)methane

Cbz-valine (2.0 g, 1 eq) was stirred at -10°C in dry THF under argon... Triethylamine. (1.11 mL/1:0 eq) was added, 5 followed by isobutyl chloroformate (1:03 ml, 1 eq). The reaction mixture was stirred for 10 min. Phenylene diamine contact (0.944 g, 1.1 eq) was added slowly in 10 mi/dry THF. The mixture was warmed to room temperature and stirred for 1 h. The solvents were evaporated and the residue partitioned between water and ethyl acetate. The ethyl acetate layer was washed with 5% aqueous sodium bicarbonate and brine. The organic layer was dried over MgSO4, filtered, and evaporated. The residue was dissolved in glacial acetic acid and heated to 65°C for 16 h. The solvents were evaporated and the residue diluted with water. After neutralizing with 31 and the saturated aqueous sodium bicarbonate, the solid was filtered and the filter cake was washed with hexane. The solid was  $\chi_{\rm col}$ ) are crystallized from ethyl acetate and hexane. S NMR (CD3OD)  $\delta$ 7.48-7.11 (9H, m), 5.06 (2H, q), 4.62 (1H, m), C2.27 (1H, m),

20 1.23 (1H, m), 1.02 (3H, d), 0.84 (3H, d).

b) (1'S)-1'-amino-1'-isopropyl-1'-(benzimidazo-2-yl) methane
The compound of Example 4(a) (2.76 g) was stirred in
methanol. 10% palladium on activated carbon (Pd/C) (250 mg)
was added and hydrogen gas was bubbled through the solution
for 1 h. The reaction was maintained under an hydrogen
atmosphere overnight. The mixture was filtered through
Celite® and the solvents evaporated to give the title
compound as a white solid (1.58 g, 98%). NMR(CDCl3) & 7.4830 7.10 (4H, m), 4.02 (1H, d), 2.24 (1H, m), 0.96 (3H, d),
0.83 (3H, d); MS(DCI/NH3) m/e 190.2 [M+H]+.1

c) (2R,4S,5S,1'S)-2-phenylmethyl-4-(t-butyldimethyl)siloxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-isopropyl-1'35 benzimidazo-2-yl]methyl-hexanamide 11 32 Rais 25

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To a solution of (2R, 4S, 5S)-2-phenylmethyl-4-(t-butyldimethyl) siloxy-5-(t-butoxycarbonyl) amino-6-phenyl-hexanoic acid (75 mg, 1.1 eq) in dimethyl formamide under

- argon, the compound of Example 4(b) (25 mg, 1.0 eq), DCC (30 mg, 1.1 eq) and HOBT (44 mg, 2.2 eq) were added. The mixture was stirred overnight, then filtered through Celite®. The solvents were evaporated and the residue was
- 5 chromatographed (silica gel, 4% methanol/dichloromethane) to give the title compound (0.070 g, 78%). NMR(CDCl<sub>3</sub>) δ 7.88 (1H, d), 7.30 (14H, m), 6.80. (1H, d), 4.93 (2H, m), 4.26 (1H, q), 4.00 (1H, m), 2.92 (7H, m), 2.01 (2H, m), 1.53 (9H, s), 1.20 (9H, s), 1.14 (6H, d), 0.41 (6H, d); MS(DCI/NH<sub>3</sub>) m/e 10 699.6 [M+H]<sup>+</sup>.
- (EMAN) (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-benzimidazo-2-yl]methyl-hexanamide
- The compound of Example 4(c) was stirred in dry THF and tetrabutyl ammonium flouride (0.6 mL, 6 eq) was added. The mixture was stirred under argon overnight at room temperature. The solution was diluted with water and extracted with dichloromethane (3X). The combined organic layers were washed with water and evaporated to a residue which was chromatographed (silica, 2% methanol/CH<sub>2</sub>CL<sub>2</sub>) to give the title compound (0.029 g, 50%). NMR(CDCl<sub>3</sub>) & 7.54 (1H, m), 7.11 (11H, m), 6.69 (4H, s), 4.98 (1H, d), 4.69 (2H, m), 3.66 (2H, m), 2.74 (5H, m), 2.31 (1H, m), 1.73 (2H, m), 1.32 (9H, s), 0.70 (6H, d); MS(DCI/NH<sub>3</sub>) m/e 585.4 [M+H]<sup>+</sup>, 413.3, 364.3, 296.2, 190.2, 173.1, 120.1.

#### Example 5

30 Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-imidazo-2-yl)methyl-hexanamide hydrochloride

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a) 2-(carbobenzyloxyamino) methyl-imidazole

(E 35:01) : Following the procedure of Example 1(a), except
substituting Cbz-glycinal for Cbz-valinal, the title compound
was prepared. NMR(CDCl<sub>3</sub>) 8 .33 (5H, s), 6.95 (2H, s), 5.95

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(1H, s(br)), 5.12 (2H, s), 4.42 (2H, d); MS(DCI/NH3) m/e

232.2 [M+H]+, 188, 171.

b) (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(tbutoxycarbonyl)amino-6-phenyl-N-(1'-imidazo-2-yl) methylhexanamide hydrochloride

Following the procedure of Example 1(b)-1(d), except substituting the compound of Example 5(a) for (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane, the title compound was prepared. NMR(CD3OD) & 7.20 (10H,m), 6.94 (2H,s), 6.11 (1H,d), 4.24 (2H,dd), 3.61 (1H,m), 3.52 (1H,m), 2.69 (4H,m), 1.66 (2H,m), 1.28 (9H,s); MS (DCI/NH3) m/e 493.7 [M+H]+, 475.7, 120.2, 98.2, 83.1, 69.1

### Example 6" The state of the sta

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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)]
methyl-hexanamide hydrochloride all the delay before the

a) (1'S)-1'-carbobenzyloxyamino-1'-methyl-1'-(imidazo-2-vl)methane

Following the procedure of Example 1(a); except substituting Cbz-alanal for Cbz-valinal; the title compound was prepared. NMR(CDCl<sub>3</sub>) δ .35 (5H,s), 6.92 (2H,s); 5.52(1H,d), 5.12 (2H,q), 4.90 (1H,q); MS(DCl/NH<sub>3</sub>) m/e 246 [M+H]+, 202, 185.

b) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)] methyl-hexanamide hydrochloride

Following the procedure of Example 1(b)-1(d), except substituting the compound of Example 6(a) for (1'S)-1'-carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane, the title compound was prepared. NMR(CD3OD) 8 7.11(10H, Em), 6.86 (2H, s), 4.69 (1H, d), 3.62 (1H, d), 3.51 (1H, m), 2.68 (6H, m), 1.59 (2H, m), 1.30 (9H, s), 1.14 (3H, d); MS(DCI/NH3) m/e 507.5 [M+H]+, 489.4, 112.1.

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a) (1'S)-1'-carbobenzyloxyamino-1'-benzyl-1'-(imidazo-2-yl)methane

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10 Following the procedure of Example 1(a), except

""" Substituting Cbz-phenylalaninal for Cbz-valinal, the title

compound was prepared. NMR(CDCl<sub>3</sub>) δ 7.37-7.05 (10H,m), .6.95

(2H, s br), 5.52 (1H, d), 5.05 (2M, s), 4.95 (1H, q), 3.32

(2H, d); MS(DCI/NH<sub>3</sub>) m/e 322, 261, 171.

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b) (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(t-s) butoxycarbonyl)amino-6-phenyl-N-(1'-benzyl-1'-(imidazo-2-yl)) methyl-hexanamide hydrochloride:

substituting the compound of Example 1(a)-1(d), except substituting the compound of Example 7(a) for (1'S)-1'- carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane, the title compound was prepared. NMR(CD3OD) & 7.15 (15H, m), 1.16.79 (2H, s), 5.78 (1H, d), 5.04 (1H, d), 3.58 (1H, m), 3.47

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A solution of (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)aminoqual4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide:(0:086-g) in trifluoroacetic acid was 35 stirred for 10 min, then was evaporated in vacuo. To the (6) i ac cresidue were added dimethylformamide, benzylchloroformate (1 deep) and triethylamine:(5 eq), and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was poured into H<sub>2</sub>O and extracted with dichloromethane. The combined organic extracts were evaporated, and the residue was triturated with diethyl ether to afford the title compound as a white solid. NMR(CD3OD) 10.7.36-6.94 (15H, m), 5.6.84 (2H, s), 4.99 (2H, s), 4.54 (2H, d) 10.3.76 (1H, m), 3.52 (1H, dd), 2.77 (5H, m), 2.04 (1H, m), 1.76 (1H, m), 1.58 (1H, m), 0.82 (3H, d), 0.66 (3H, d).

Example 9 chedison(I)

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4.5-dimethyl)imidazol-2yllmethyl-6-phenyl-2-phenylmethyl-hexanamide(3,113)

131 477 MS (00 (/XH3) milk 27 % 7 %)

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a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4,5-dimethylimidazol-2-yl)methane

Cbz-Valinal (4.14 g) was stirred in methanol with 2,3-butanedione (1.54 mL, 1.0 eq). Ammonia was bubbled through the solution at -25°C for 5 min. The cooling bath was

- removed and the mixture allowed to warm to 20°C. The solution was stirred for 16 h under Ar. The solvents were removed by rotary evaporation, and the residue was diluted with dichloromethane and extracted with dilute aqueous HCl. The organic layer was concentrated to afford unreacted Cbz-
- valinal (4.02 g). The acidic aqueous layer was basified with 1N NaOH and extracted with dichloromethane, the organic extract was concentrated and the residue purified by flash chromatography (4% methanol in dichloromethane) to provide the title compound as a white solid (50 mg). NMR(CD<sub>3</sub>OD) δ
- 30 7.29 (5H, m), 5.04 (2H, dd), 4:38:(1H, d); 2:06:(6H; s); 2.01 (1H, m), 0.93 (3H, d), 0.77 (3H, d).
- -(-fylacub) (18)-1-(4,5-dimethylimidazol-2-yl)-2-methylpropylamine
- hydrogenolysis using the same procedure as described of previously in Example 1(b), except using the product of 1(a) (50 mg), to afford the title compound as a white solid

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- 2.06 (6H, s), 2.00 (1H, m), 0.71 (6H, dd).
  - c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t
    '5 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4,5-dimethyl)

    imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

Using the procedure of Example 1(c), except substituting (2R,4S,5S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-

6-phenyl-2-phenylmethylhexanoic acid and (1S)-1-(4,5-

dimethylimidazol-2-yl)-2-methylpropylamine (24 mg), the title compound was prepared (55 mg, 57%). NMR(CDCl3) δ 7.26-6.80

(10H, m), 4.65 (1H, d), 4.24 (1H, dd), 3.87 (1H, q), 3.61

(1H, m), 2.77-2.39 (5H, m), 2.22 (1H, m), 1.98 (6H, s), 1.79

13.6 (1H, m), 1.58 (1H, m), 1.24 (9H, s), 0.85 (9H, s), 0.69 (6H, 5), 0.66 (6H, 6d).

d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4, 5-dimethyl) imidazol-2-yl] methyl-6-phenyl-2-phenylmethyl-hexanamide

By following the deprotection procedure described in Example 1(d), except using (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4,5-dimethyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (55 mg) and omitting the final

25 treatment with methanolic HCl, the title compound was prepared (25 mg, 62%). NMR (CDCl<sub>3</sub>) δ 7.29-6.88 (10H, m), 4.98 (1H, br d), 4.47 (1H, m), 4.29 (1H, m), 3.58 (2H, m), 2.84-2.51 (5H, m), 2.20 (1H, m), 2.04 (6H, s), 1.71 (2H, m), 1.38

(9H, s), 0.69 (6H, dd).

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#### Example 10

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl) amino-4hydroxy-N-[1'-isopropyl-1'-(4.5-dimethyl) imidazol-2-

35 <u>vllmethyl-6-phenyl-2-phenylmethyl-hexanamide</u>

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a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-phenylimidazol-2-yl)methane

Using the procedure of Example 1(a), except using Cbz-(L)-valine (2.19 g) and α-ketophenylacetaldehyde instead of glyoxal, the title compound was prepared (1.54 g, 48%). NMR(CDCl<sub>3</sub>) δ 7.62 (1H, (br)), 7.24 (10H, m), 5.79 (1H, d), 5 5.04 (2H, dd), 4.32 (1H, dd), 2.31 (1H, m), 0.96 (3H, d), 0.79 (3H, d); MS m/e 350.4 [M+H]<sup>+</sup>, 199.0.

b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t- nobutyldimethylsiloxy-N-[1'-isopropyl-1'-(4-phenyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

Using the procedure of Example 1(b)-1(c), except using the compound of 10(a) (72 mg), the title compound was prepared (67 mg, 44%). NMR(CDCl<sub>3</sub>) & 7.70 (1H, d), 7.40-6.71 (16H, m), 4.73 (1H, d), 4.54 (1H, dd), 3.96 (1H, q), 3.69 (1H, m), 2.88-2.36 (5H, m), 1.73 (2H, m), 1.33 (9H, s), 0.91 (9H, s), 0.84 (6H, dd), 0.11 (6H, d); MS m/e 725.4 [M+H]+.

c) (2R, 4s, 5s, 1's)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-phenyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

14. (14. 1) B. (6. 1. 16. 16. 18. 18. 18. 19.

Using the procedure of Example 9(d), except starting from (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-phenyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (67, mg), the title compound was prepared (30 mg, 54%). NMR(CDCl3) & 7.52-6.67 (16H, m), 5.48 (1H, d), 3.60 (1H, q), 3.44 (1H, d), 2.60 (4H, m), 1.96 (1H, m), 1.62 (2H, m), 1.23 (9H, s), 0.73 (3H, d), 0.62 (3H, d); MS m/e 611.4 [M+H]+, 242.2, 195.0, 150.2.

#### Example 11

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(N'-methyl)imidazol-2-yllmethyl-6phenyl-2-phenylmethyl-hexanamide

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a) (1S)-carbobenzyloxyamino-1-isopropyl-1-(N'-methylimidazol-2-yl)methane
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at 40°C for 2 h in methyl iodide (5 mL). The reaction

- 5 mixture was evaporated, and the residue was suspended in aqueous Na<sub>2</sub>CO<sub>3</sub>. The mixture was extracted with
- product was purified by flash chromatography (silica, 2% methanol/dichloromethane) to yield the title compound (200
  - 10 mg, 70%). NMR (CDCl<sub>3</sub>)  $\delta$  7.29 (5H, 8), 6.92 (1H, 8), 6.69 (1H, 8), 5.94 (1H, d), 5.03 (2H, q), 4.55 (1H, dd), 3.64 (3H, s),

Barrier and I

A Miles one 2.20 (1H, m), 1.01 (3H, d), 0.82 (3H, d), 10 (70)

of the first the many however by the state of the de-

- ac & b): (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-.:
- , ipo 15 butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-methyl)imidazol-2-
- rot propertyl-6-phenyl-2-phenylmethyl-hexanamide or pro-
- using the compound of 11(a) (90 mg), the title compound was prepared (104 mg, 50%). NMR (CDCl<sub>3</sub>) & 7.32-6.89 (10H, m),
- back 20 of 6.81 (1H, s), 6.59 (1H, s), 6.08 (1H, d), 4.71 (2H, m), 3.94 (1H, q), 0.3.70 (1H, m), 3.25 (3H, s), 2.80-2.36 (5H, m), 2.21 (7 (1H, m), 1.73 (2H, m), 1.31 (9H, s), 0.94 (9H, s), 0.85 (6H, dd), 0.11 (6H, s).
  - 2513cc) (2R, 4S, 5S, 1.S) -5= (t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1.a.(N(=methyl) imidazol-2-yl]methyl-6-phenyl-2-yphenylmethyl-hexanamide (48) base and 3130 aft
- mora (882 % diFollowing the procedure of Example 9(d), except using (801) 01(2R, 4S 5S, 1!S)-5-(t-butoxycr-bonyl) amino-4-t-38 483
  - (30 % butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-methyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (100 mg), the title compound was prepared (74 mg, 89%). NMR(CDCl<sub>3</sub>) δ 7.21-6.74 (11H, m), 6.70 (1H, s), 6.59 (1H, s), 4.95 (1H, d), 4.61 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, m), 3.48 (3H, s), 2.71 (5H, m), 2.06 (1H, dd), 3.60 (3H, dd), 3.60 (3H,
  - 35 m), 1.64 (2H<sub>ch</sub>(m)<sub>fert</sub>1.32 (9H<sub>ch</sub>(s), 0.82 (3H, d), 0.63 (3H, d); - antitut MS<sub>c</sub>m/e 549.3 [M+H]+1 for a minimum on a grain (1)

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# Example 12 add to the 10 state

Preparation of (2R,4S,5S,1'S)-5-(t-butoxycarbonvl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-v1)methyl-6-phenyl-2-(3-phenylpropargyl)hexanamide be so gave gove as each

er and a rest in the

a) (3R,5S,1'S) - (1'-t-butoxycarbonylamino-2'-phenyl) ethyl-3-(3-phenylpropargyl)-tetrahydrofuran-2-one see destabling

To a solution of lithium disopropylamide (3:61 mL, 2.0 M in THF, 2.2 eq) in THF at -78°C under an argon atmosphere, (5S,1'S)-(1'-t-butoxycarbonylamino-2'-2 phenyl) ethyl-tetrahydrofuran-2-one (1.0 /g, 1.0 eq) was added. After stirring at -78°C for 15 min, hexamethylphosphoramide (1.14 mL, 2 eq) was added, and stirring was continued an ended is additional 10 min. Phenylpropargyl bromide (1:28 g, 2:0 eq), was added and the resulting mixture was stirred at -78°C for 2 h, then poured into dilute aqueous HCl and extracted with dichloromethane. The combined organic extracts were evaporated under reduced pressure to an oil, which was chromatographed (silica, 20% ethyl acetate/hexanes) to afford · 7 20 the title compound as a white solid (0.455 g, 33%) NMR(CDCl<sub>3</sub>) δ 7.18 (10H, m), 4.50 (2H, m); 3.93 (1H, q), 2.79 (5H, m), 2.23 (2H, m), 1.24 (9H, s). (H), 11.4 (1H)

> b) (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-(3-phenylpropargyl) hexanoic acid

The title compound (496 mg, 84%) was prepared by the procedure of Evans et al., J. Org. Chem: 50,14615 (1985) from the product of 12(a) (450 mg).... NMR (CDCl3),  $\delta$ .7.49-7.10 (10H, m) , 4:71 (1H, d) , 3:94 (3H, m) , 2:69 (4H, m) , 1:590 (2H, m) ,

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1.31 (9H, s), 0.89 (9H, s), 0.11 (6H, d); 3-1 (635)

c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-i'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenylpropargyl) hexanamide (3) (3) (4)

Following the procedure of Example 1(c), except using (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-(3-phenylpropargyl) hexanoic acid (240 mg) and

(1S)-1-imidazol-2-yl-2-methylpropylamine, the title compound was prepared (244 mg, 84%). NMR(CDCl<sub>3</sub>) & 7.14 (12H, m), 6.72 (1H, d), 4.58 (1H, d), 4.49 (1H, dd), 3.92 (1H, q), 3.80 (1H, m), 2.54 (5H, m), 1.65 (2H, m), 1.20 (9H, s), 0.81 (9H, s), 0.80 (6H, dd), 0.05 (6H, d).

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- d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(3phenylpropargyl) hexanamide
  - 10 :: Following the procedure of Example 9(d), except using (2R, 4S, 5S, 1'S) = 5 (t-butoxycarbonyl) amino-4-t-
- butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl6-phenyl-2-(3-phenylpropargyl)hexanamide, the title compound
  (1()) was prepared (161 mg, 79%). NMR(CDCl<sub>3</sub>) δ 7.24-6.98 (10H, m),
  (11) 615 6.68 (2H, 3s), 5.20 (1H, m), 4.52 (1H, d), 3.49 (2H, m), 3.06
  (1H, m), 2.56 (5H, m), 12.04 (1H, m), 1.61 (2H, m), 1.26 (9H, s), 0.68 (6H, dd); MS m/e 581.2 (M+Na)+, 559.2 [M+H]+, 541.4, 503.2, 485.2, 459.2, 441.2.

Setyr B. Sefyther by Example 13: Security

Preparation of (2R.4S.5S.1'S)-5-(isopropoxycarbonyl) amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethyl-hexanamide

4.1 4.20 (1.14) (1.15) (1.15) (1.15) (1.15)

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- (1'-
- isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl
  - public hexanamide being super adapt of the a lateries as and
- yet Lothing and The product of Example 1(c) (0.20 g, 0.31 mmol) was
- with toward the dissolved in strifluoroacetic acid and stirred at room of
- -36 C % (stemperature for 5 min, and partitioned between accept
- (fig.) a dichloromethane and saturated aqueous Na<sub>2</sub>CO<sub>3</sub>. The organic
- which the extract was dried over Na<sub>2</sub>CO<sub>3</sub>, filtered and evaporated to
- 103 St. : afford the title compound (0.17 g, 100%) which was used
  - - b) (2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-

isopropoxycarbonyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

A mixture containing the compound of 13(a) (0.17 g, 0.31 mmol), isopropyl chloroformate (0.62 mL, 114 in the

- dichloromethane, 2 eq) and 4-dimethylaminopyridine (0.75 g, 2 eq) in dichloromethane (40 mL) was allowed to stir at room temperature overnight under an argon atmosphere. The mixture was then partitioned between dichloromethane and saturated aqueous Na<sub>2</sub>CO<sub>3</sub>, and the organic extract was dried over Na<sub>2</sub>CO<sub>3</sub>.
- The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 44.6) methanol/dichloromethane) to afford the title compound (0.214 g, 96%). NMR (CDCl<sub>3</sub>) δ(7.35-6.78 (12H, m), 6.57 (1H, d), 5.61 (1H, dd), 5.19 (1H, m), 4.86 (1H, m), 4.77 (1H, d), 3.97 (1H, d), 3.63 (1H, t), 2.88 (1H, dd), 2.70-2.48 (4H, m), 2.06 (1H, m), 2.00-1.85 (1H, m), 1.79-1.64 (1H, m), 1.45 (6H, dd), 0.94 (9H, s), 0.85 (6H, d), 20.12 (6H, d), 3.97 (2)
  - c) (2R,4S,5S,1'S)-5-(isopropoxycarbonyl)amino-4-hydroxy-N20 (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

methanol, excess aqueous HCli(~5 eq) was added. The resulting solution was allowed to stir at room temperature

- overnight, and was concentrated under reduced pressure. The residue was diluted with H2O, and basified with aqueous Na<sub>2</sub>CO<sub>3</sub>. The mixture was extracted with dichloromethane, and the combined organic extracts were dried over Na<sub>2</sub>CO<sub>3</sub>. The solvent was removed (in vacuo, and the residue was purified by
  - flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (0.150 g; 97%) ar NMR (CDCl3) δ 7.32-
  - 76.96 (13H, m), 5.48 (1H, d), 5.08 (1H, m), 5.00 (1H, s(br)),
    - 4.87 (1H, m), 3.78 (1H, m), 3.62 (1H, m), 3.25 (1H, m), 2.96-2.67 (4H, m), 2.29 (1H, m), 1.95-1.65 (2H, m), 1.25-1.12 (6H,
  - 35 dd), 0.80-0.60 (6H, dd); MS m/e 521 [M+H]+, 519 (M-H) 38

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5 (5) (8 **9** 66 (3 1**36** (5 14 **3**5)

2 (201) d): (2R,4S,5S,1'S)-5-(isopropoxycarbonyl) amino-4-hydroxy-N-

ear Charles on phenylmethyl-hexanamide hydrochloride on the second of th

OSS win methanoly (10 mL) and a 1M solution of RCl in other (0.192 mm) was added. The solution was concentrated by rotary

for the red evaporation without heating, and the residue was trituated

OF (with ether and dried under vacuum to afford the title.

3:.7 (compound (104 mg, 98%) 3:.7 NMR(CD<sub>3</sub>OD)  $\delta$  7.30 (2H, s), 7.21-

10 .6.88(10H, m), 4.61 (2H, m), 3.65 (1H, m), 3.48 (1H, d), 2.99

ANS: VELA (1H, m), 2.87 (1H, m), 2.74-2.56 (2H, m), 2.12 (1H, m), 1.75-

(H (1) 1.50 (2H, m), 1.17-1.00 (6H, dd), 0.90 (3H, d), 0.64 (3H, d).

#### Example 14

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10 Mar N. L. 100 (20) 18:00 (a)

Preparation of (2R,4S,5S,1'S)-5-(benzyloxyethoxycarbonyl)

amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethyl-hexanamide

20 a) benzyloxyethyl-(4-nitro)phenylcarbonate

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To Ca solution of 2-benzyloxyethanol (2.5 g, 16.4 mmol)

 $^{2}$   $^{28}$   $^{28}$  and bis(4-nitrophenyl)carbonate (5.0 g, 1 eq) in

was added. The resulting mixture was allowed to stir at room

- 25 temperature for 3 d. The reaction mixture was washed successively with H2O and saturated aqueous NaCl and dried over Na2SO4. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 20% methyl acetate/hexanes) to afford the title compound (4.38 g,
  - 30 84%). NMR(CDCl<sub>3</sub>) δ 8.26 (2H, m), 7.34 (7H, m), 4.62 (2H, s), 4.49 (2H, t), 3.70 (2H, t).

b) (2R, 4S, 5S, 1!S) -5- (benzyloxyethoxycarbonyl) amino-4-t-i visconing butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-benzyloxyethoxy35 carbonyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-6

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Tota solution of the compound of Example 14(a) (134.5) mg, 0.24 mmol) in dichloromethane (40 mL) under an argon

atmosphere, benzyloxyethyl 4-nitrophenyl carbonate (160 mg, 2 eq) and 4-dimethylaminopyridine (60 mg/20 eq) were added. The resulting mixture was allowed to stir at room temperature overnight, and wasadiluted with dichloromethane. The organic extract was washed successively with aqueous Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, aqueous Na<sub>2</sub>CO<sub>3</sub> and H<sub>2</sub>O, and dried over Na<sub>2</sub>CO<sub>3</sub> w The solvent be . . . . was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (180 mg, 82%). NMR (CDCl<sub>3</sub>)  $\delta$  7.45-他 10 .6.80%(22H, m), 6.62%(1H, d), 5.60%(1H, t), 5.06%(1H, d), 4.60 (2H, s), 4.52 (2H, s), 4.50 (2H, m), 4.31 (1H, m), 4.07 (2H, (i) (iii) (m), 3.80 (2H, t), 3.68 (1H, q), 3:57 (1H, q), 2:85 (1H, m), 2.77-2.41 (4H, m), 2.09 (1H, m), 1.90 (1H, m), 1.73 (1H, m), 0.95 (9H, s), 0.81 (6H, dd), 0.11 (6H, d).

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10 L 10

c) (2R,4S,5S,1'S)-5-(benzyloxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

Following the procedure of Example 13(c) , except using the compound of Example 14(b) +(160 mg); the title (compound was prepared (100 mg, [81%). NMR(CDCl<sub>3</sub>, CD<sub>3</sub>OD)  $\delta$  7.40-6.79 (17H, m), 4.55 (2H, s), 4.45 (1H, ed), 4.20 (2H, m), 3.80-3.45 (5H, m), 2.95-2.66 (4H, m), 2.59 (1H, dd), 2.07 (1H, m), 1.71 (2H, m), 0.80 (3H, d), 0.68 (3H, d). .... webble use:

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### Example 15 provide the stroops

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6.49 (28, 8), 0.76 (28, 87)

Preparation of (2R.4S.5S.1'S)-5-(methoxycarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-

. 30 phenylmethyl—hexanamide at 100.3 能 (+ (340) 25数 。 資料

a) (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1!-isopropyl-1!-(N'-), N. . (4) methoxycarbonyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-35 hexanamide and Ly-1-10 shim (Ly-1-10 shim)

Following the procedure of Example 13(b) except using (2R, 4S, 5S, 1'S) -5-amino-4-t-butyldimethylsiloxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-

- hexanamide, the title compound was prepared (89%).

  NMR(CDCl<sub>3</sub>) & 7.40-6.79 (12H, m), 6.52 (1H, d), 5.58 (1H, dd),

  4.91 (1H, d), 3.96 (3H, s), 3.95 (1H, d), 3.66 (1H, t), 3.60

  (3H, s), 2.85 (1H, m), 2.73-2.40 (4H, m), 2.08 (1H, m), 1.90

  5 (1H, m), 1.69 (1H, m), 0.95 (9H, s), 0.85 (6H, dd), 0.14 (6H, d)
  - b) (2R, 4S, 5S, 1'S)-5-(methoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 13(c), except using the compound of Example 15(a), the title compound was prepared (70%). NMR(CDCl<sub>3</sub>, CD<sub>3</sub>OD) δ 7.23-6.60 (12H, m), 4.38 (1H, d), 3.65 (1H, t), 3.54 (3H, s), 3.33 (1H, m), 2.95 (1H, 15 m), 2.82-2.40 (4H, m), 1.95 (1H, m), 1.64 (2H, m), 0.69 (6H, dd).

### Example 16

- 20 Preparation of (2R.4S.5S.1'S)-5-(ethoxycarbonyl)amino-4
  (c) hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide
  - a) (2R, 4S, 5S, 1'S) 5 (ethoxycarbonyl) amino 4 t -
  - 25 butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-

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(c) for collection with the control

- with the ethoxycarbonyl) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-1 hexanamide of ( ) the care of the control of the con
- procedure of Example 13(b), except using a (2R, 4S, 5S, 1'S) = 5-amino-4-t-butyldimethylsiloxy-N-(1'-
- 26.30 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
- (NI) C3. Shexanamide and ethylchloroformate, the title compound was
- d), 5.60 (1H, dd), 4.86 (1H, d), 4.41 (2H, m), 4.15-3.90 (3H,
  - m), 3.66 (1H, t), 2.87 (1H, m), 2.75-2.45 (4H, m), 2.08 (1H,
  - 35 m), 1.92 (1H, m), 1.70 (1H, m), 1.45 (3H, t), 1.18 (3H, t), 0.98 (9H, s), 0.85 (6H, dd), 0.13 (6H, d).

b) (2R, 4S, 5S, 1'S) -5-(ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 13(c), except using the compound of Example 16(a), the title compound was prepared (95%). NMR(CDCl<sub>3</sub>, CD<sub>3</sub>OD) δ 7.25-6.75 (12H, m), 4.43 (1H, d), 3.95 (2H, q), 3.61 (1H, q), 3.40 (1H, m), 2.85 (1H, m), 2.80-2.40 (4H, m), 2.05 (1H, m), 1.61 (2H, t), 1.11 (3H, t), 0.72 (3H, d), 0.55 (3H, t).

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-propenyl)hexanamide (2) 04 3-28.

a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-(3-phenylprop-2-enyl)-tetrahydrofuran-2-one

Following the procedure of Example 12(a), except using cinnamyl bromide (0.485 mL) as the alkylating agent, the title compound was prepared (0.51.g, 75%). NMR(CDCl<sub>3</sub>) δ 7.35-7.10 (10H, m), 6.43 (1H, d), 6.09 (1H, m), 4.60 (1H, m), 4.48 (1H, q), 4.00 (1H, t (br)), 2.96-2.55 (4H, m), 2.53-2.21 (2H, m), 2.05 (1H, m), 1.35 (9H, s).

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b) (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethyl-siloxy-6-phenyl-2-(3-phenyl-2-propenyl)hexanoic acid

Following the procedure of Example 12(b), except using the compound of Example 17(a), the title compound was prepared (77%). NMR(CDCl<sub>3</sub>) & 7.40-7.05 (10H, m), 6.48-6.00 (4H, m), 4.78 (1H, d), 3.94 (1H, q), 3.80 (1H, m), 2.89 (1H, m), 2.83-2.26 (4H, m), 1.90 (1H, m), 1.59 (1H, m), 1.28 (9H, s), 0.90 (9H, s), 0.08 (6H, d).

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butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-propenyl)hexanamide
```

Following the procedure of Example 1(c), except using 5 to the compound of, 17(b), the title compound was prepared (82%).

NMR (CDCl<sub>3</sub>); δ 7.35-7.15 (10H, m), 7.14-6.85 (2H, m), 6.73 (1H,

han hads t), 3.97 (1H, q), 43.76 (1H, m), 2.77 (2H, d), 2.50-2.25 (2H,

Hq = 2 m), 2.12 (1H, m), 61.70 (1H, m), 1.63 (1H, m), 1.36 (9H, s), 10 0.92 (9H, s), 0.81 (6H, d), 0.09 (6H, d). 5 5 5 5 5 5

of the last commence by the distance of the second of the second of the second of

d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2is) 07.5 propenyl)hexanamide (60.) 5-3 (1.0.85) (2.0.0.00)

15.31) Following)the procedure of Example 9(d), except using the compound of 17(c), the title compound was prepared (90%).

NMR(CDCl<sub>3</sub>, CD<sub>3</sub>OD) & 7.30-7.00 (10H, m), 6.71 (2H, s), 6.26

(1H, d), 6.41 (1H, m), 3.66 (1H, d), 3.50 (1H, d), 2.88-2.45

(4H, m), 2.36 (1H, m), 2.23 (1H, m), 2.06 (1H, m), 1.70 (2H,

20 m), 1.34 (9H, s), 0.88 (3H, d), 0.74 (3H, d) ) in all dd.0 (get MS m/el/561 (M+H)+1 ) a bennagana odd to am daen f

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl) amino-4
b Wehydroxy-N-[1'-isopropyl-1'-(4-nitroimidazol-2-yl)] methyl-6
phenyl-2-phenylmethyl-hexanamide

```
(1H, m), 1.98 (3H, s), 20.98 (3H, d, J=5, 3°Hz), 0.82 (3H, d, -1) (1 J=5 Hz). 1 (2 J=5, 3°Hz), 0.82 (3H, d, d, -1) (1 J=5 Hz). 1 (3H, d, -1) (2 Hz) (2 J=5, 3°Hz), 1 (3Hz) (3H
```

- b) (1S)-N-(1-(4-nitroimidazol-2-yl)-2-methyl) propylacetamide

  The compound of Example 18(a) (290 mg;q:1:60 mmol) was

  dissolved in cold concentrated H<sub>2</sub>SO<sub>4</sub> (2 mL) (and after

  stirring for 15 min, 90% HNO<sub>3</sub> (0.4 mL) was added dropwise.
- The resulting mixture was slowly warmed to 40°C and stirred to 10°C and stirred to 10°C and the pH
- was adjusted to 4 by the addition of solid NaHCO3. The mixture was extracted with ethyl acetate (6x), and the combined organic extracts were dried over MgSO4 and concentrated under reduced pressure to afford the title
  - compound (153 mg, 42%). NMR (CD3OD) 5 7.98; (1H, s), 4.70 (1H, 15 d, J=6 Hz), 2.35-2.15 (1H, m), 1.98; (3H, s), 30.95 (3H, d, J=5
- 15 d, J=6 Hz), 2.35-2.15 (1H, m), 1.98 (3H, 65), 20.95 (3H, 6, J=5 Hz); MS m/e 475.2 (2M+Na)+, 249.2 (M+Na)+, 227.2 [M+H]+, 185.2 168.0 (30) (50)

(14, d), 6, or the the the first of the first

- (1S)-1-(4-nitroimidazol-2-yl)-2-methylpropylamine,
  - 20 dihydrochloride salt (n. (84) 88.0 (m. (8) \$8.5 .(8)

A mixture of the compound of Example 18(b) 6(153 mg, 0.68 mmol) in 6N HCl (2 mL) was heated at 90°C for 12 h, cooled and concentrated under reduced pressure. The title compound was obtained (138 mg, 80%) and used without further purification., NMR(CD3OD) δ 8.12 (1H; s), 64:30 L(1H; d, J=4

Hz) / 2.45-2.30 (1H, m) / 1.12 (3H, d, d, J=4 Hz) / 0.90 / (3H, d, J=4 Hz).

- d) (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-t-; (1)
- butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-nitroimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide(5)

Following the procedure of Example 1(c), except using

(2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy6-phenyl-2-phenylmethylhexanoic acid and (1S)-1-(4-3)

nitroimidazol-2-yl)-2-methylpropylamine, the title compound was prepared. NMR(CDCl<sub>3</sub>), 8,7.30-6.90, (10, H, J, m); 6.60) (1H, d, J=4 Hz), 4.70 (1H, d, J=5 Hz), 4.40; (1H, t, J=4 Hz), 3.90 (1H, q, J=4 Hz), 3.75 (1H, dd, J=8, 3 Hz), 2075-2.30 (6H, m),

1.80-1.50 (2H, m), 1.25 (9H, s), 0.85 (9H, s), 0.70 (6H, m), 0.05 (6H, d, J=4 Hz).

The state of the s

- (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
- Following the deprotection procedure of Example 1(d),
  except using the compound of Example 18(d), the title
  compound was prepared. NMR(CD<sub>3</sub>OD) δ 7.90 (1H, s), 7.40-6.90
  (10H, m), 4.53 (1H, d, J=6 Hz), 3.70 (1H, m), 3.50 (1H, m),
  - 2.90-2.60 (5H, m), 2.00 (1H, m), 1.90-1.55 (2H, m), 1.49 (9H, s), 0.85 (3H, d, J=4 Hz), 0.70 (d, 3H, J=4 Hz); MS m/e 602.4 (M+Na)+, 580.4 [M+H]+, 524.4, 480.4.

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#### Example 19

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-(1'-ethyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

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a) (1S)-1-carbobenzyloxyamino-1-ethyl-1-(imidazol-2-yl)methane

Following the procedure of Example 1(a), except using Cbz-(L)-α-ethylglycinal in place of valinal, the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 7.45-7.10 (5H, m), 6.90 (2H, s), 5.65 (1H, d, J=6 Hz), 5.10-4.95 (2H, m), 4.40 (1H, q, J=5 Hz), 2.00-1.70 (2H, m), 1.00-0.80 (3H, m).

in the b) (1S)-(1-imidazol-2-yl)propylamine

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30 Following the procedure of Example 1(b), except using the compound of Example 19(a), the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 6.90 (2H, s), 5.00-4.50 (2H, br s), 4.00 (1H, t, J=5 Hz), 2.00-1.70 (2H, m), 1.00-0.80 (3H, m).

- c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-ethyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 1 (c), except using

  (2R, 4S, 5S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy6-phenyl-2-phenylmethylhexanoic acid and the compound of
  Example 19(c), the title compound was prepared. NMR (CDCl<sub>3</sub>) δ

  7.35-6.90 (10H, m), 6.78 (2H, s), 6.20 (d, J=5, Hz), 4.80-4.65

  (2H, m), 4.05 (1H, q, J=5 Hz), 3.72 (1H, dd, J=10, 3 Hz),

  10 2.90-2.50 (5H, m), 2.10-2.05 (1H, m), 1.90-1.65 (3H, m), 1.40

  (9H, s), 0.95 (9H, s), 0.90-0.85 (3H, m), 0.50 (6H, s).
  - d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-ethyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-
- 15 hexanamide

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Following the procedure of Example 9(d), except using the compound of Example 19(c), the title compound was prepared. NMR(CD3OD) & 7.40-7.00 (10H, m), 6.85 (2H, s), 3.60-3.50 (2H, m), 2.95-2.60 (5H, m), 1.95-17.52 (4H, m), 1.48-1.26 (9H, m), 0.8-0.9 (3H, m).

MS m/e 521.2 [M+H]+; 503.4, 447.4.

#### 

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- Following the procedure of Example 19(a)-19(d), except substituting Cbz-(L)-α-propylglycinal for Cbz-(L)-α- gethylglycinal, the title compound was prepared. Data for the intermediates of this synthesis were:

1.8 (4<del>5)</del> 5-3 (5 (5-3) 36

```
(1S)=1-carbobenzyloxyamino-1-propyl-1-(imidazol-2-yl)methane. NMR(CDCl3) & 7.40-7.10 (10H, m), 6.65 (2H, s), 5.10-4.90 (2H, m), 4.65 (1H, q, J=5 Hz), 2.05-1.93 (1H, m), 1.90-1.75 (1H, m), 1.45-1.20 (4H, m), 6.65 (3H, m), 6.65 (3H, m), 6.65 (2H, s), 6.65
```

b) (1S)-1-(imidazol-2-yl)butylamine. NMR(CDCl<sub>3</sub>) δ 6.90 (2H, -s), 5.10-4.40 (2H, s(br)), 4.05 (1H, t, J=5 Hz), 1.90-1.55 (2H, m), 1.45-1.20 (4H, m), 0.95-0.80 (3H, m).

- 6.c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-propyl-1'-imidazol-2-yl]methyl-6phenyl-2-phenylmethyl-hexanamide. NMR(CDCl<sub>3</sub>) δ 7.35-7.00 (10H, m), 6.78 (2H, s), 6.22 (1H, d, J=5 Hz), 4.85-4.68 (2H, m), 4.00 (1H, q, J=3 Hz), 3.75 (1H, dd, J=10, 3 Hz), 2.80-2.50 (5H, m), 2.12-1.95 (1H, m), 1.90-1.60 (3H, m), 1.40-1.20 (13H, m), 0.90 (9H, s), 0.87-0.80 (3H, m), 0.07 (6H, s).
  - d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-20 propyl-1'-imidazol-2-yl] methyl-6-phenyl-2-phenylmethyl-hexanamide. NMR(CD3OD) δ 7.40-7.00 (10H, m), 6.90 (2H, s),
     3.78-3.50 (2H, m), 2.90-2.60 (5H, m), 1.90-1.55 (4H, m),
     1.45-1.20 (13H, m); MS m/e 535.4 [M+H]<sup>+</sup>.

# . www. 25 ivilian in greaters of the time Example 21 speeds of the second

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hydroxy-N-[1'-isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

(HP) (18 a) (18)-N-1-(4-bromoimidazol-2-yl)-2-methylpropylacetamide

(30° ) () IT I ((33 1-4) (3 1 ) ) (31 3 1 ) (1 1 4 ) (3 1 )

4) 41 (2.) but ham, a constable at only length by .

(1S)-N-1-(4,5-dibromoimidazol-2-yl)-2-methylpropylacetamide

35-S methylpropylacetamide (1.58 g, 8.73 mmol) in 95% ethanol (30 mL), 2,4,4,6-tetrabromocyclohexadienone (3.93 g, 9.60 mmol) was added. The resulting mixture was stirred at room temperature for 30 min, and was concentrated in vacuo. The

residue was dissolved in dichloromethane; washed with aqueous NaHCO3 and dried over Na2SO4. The solvent was removed in vacuo, and the residue was purified by flash chromatography (1) . (1) 3 to afford the title compound (650 mg, 29%) 10 NMR (CDCl3) δ

5 7.70 (1H, d, J=7 Hz), 6.85 (1H, s), 4.67% (1H, t), J=7 Hz), 2.35-2.25 (1H, m), 1.95 (3H, s), 1.05 (3H, d, J=5 Hz), 0.80 

Also isolated was (1S)-N-1-(4,5-dibromoimidazol-2-yl)-2methylpropylacetamide (50 mg, ::8%): : NMR (CDCl3), δ.4.68 (1H, t, J=7 Hz), 2.38-2.25 (1H, m), 2.05 (3H, s), 1.05 (3H, d, J=5

Hz), 0.85 (3H, d, J=5 Hz); MS m/e 340:0 [M+H] +, 280.8.

intributes their toxy is foregoing the attack of the contribution of the contribution

b) (1S)-1-(4-bromoimidazol-2-yl)-2-methylpropylamine, dihydrochloride (10%, m), 6 70 (2%, s)

Following the procedure of Example 18(c), except using (1S)-N-1-(4-bromoimidazol-2-yl)-2-methylpropylacetamide, the title compound was prepared. NMR(CD3OD) & 7.60 (1H, s), 4.35 (1H, d, J=7 Hz), 2.50-2.38 (1H, m), 1.10 (3H, d, J=5 Hz), 0.82 (3H, d, J=5.Hz). op (200. a) (1 18 1 4,6 14 ,64) (6)

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c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t- 9 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-bromoimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1(c), except using (2R, 4S, 5S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-25 6-phenyl-2-phenylmethylhexanoic acid and (1S)-1-(4bromoimidazol-2-yl)-2-methylpropylamine dihydrochloride, the title compound was prepared. NMR(CDCl3) & 7.40-7.00 (10H, m), 6.70 (1H, s), 6.45 (1H, d, J=5 Hz), 4.80 (1H, d, J=6 Hz),

4.40 (1H, t, J=5 Hz), 4.02 (1H, q, J=4 Hz), 3.78 (1H, dd, J=7, 2 Hz), 2.90-2.30 (9H, m), 1.85-1.60 (2H, m), 1.45 (9H, s), 1.00 (9H, s), 0.85 (6H, t, J=4 Hz), 0.10 (6H, d, J=6 Hz).

d) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-

- - - 1. Salta S., artists - 1. 3 - 1- M-(21) .

isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-ag phenylmethyl-hexanamide or representation (1906) (1906)

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Following the procedure of Example 9(d) except using (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1!-isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide, the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 7.40-7.00 (10H, m), 6.70 (1H, s), 6.55 (1H, m), 4.90 (1H, d, J=5 Hz), 4.50 (1H, t, J=5 Hz), 3.75-3.55 (2H, m), 2.95-2.65 (5H, m), 2.40-2.25 (1H, m), 1.90-1.60 (2H, m), 1.48 (9H, s), 0.80 (6H, t, J=6 Hz). MS m/e 613.2 [M+H]+; 535.2.

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### Example 22

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4.5-dibromoimidazol-2-yl)]methyl6-phenyl-2-phenylmethyl-hexanamide

(i.e. 15) formed for all beyond it. Second for (18) -18(d), and (19(d), sexcept substituting (18)-N-1-(4,5-dibromoimidazol-2-conditions (19)-2-methylpropylacetamide for (18)-N-(1-4-nitroimidazol-2-conditions (19)-2-methylpropylacetamide, the title compound was prepared.

Analytical data for the intermediates of this synthesis were:

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a) (1S)-1-(4,5-dibromoimidazol-2-yl)-2-methylpropylamine, 2H 1 dihydrochloride: NMR(CD3OD), 8 4.10-3.90 (1H, br s), 2.30-2H 1 d 2.10 (1H, s(br)), 1.10 (3H, d, J=5 Hz), 0.85 (3H, d, J=5 Hz).

bias c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-35 a isopropyl-1'-(4,5-dibromoimidazol-2-yl)] methyl-6-phenyl-2-, (phenylmethyl-hexanamide. NMR(CDCl3) & 7.35-6.85 (10H, m), 6.65 (1H, br s), 4.92 (1H,1d, J=4 Hz), 4.50 (1H, m), 3.72-, 3.50 (2H, m), 2.98-2.63 (5H, m), 2.15-2.02 (1H, m), 1.90-1.70

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(2H, m), 1.40 (9H, s); MS m/e 693.03[M+H]+; 637, 619, 593, phones of his and specially as in the prepared the foots of the

of the two later only being the back

S. T. D. ale. Example 23 (HS) 38-1-87-8 1. 10 per 100 said (mr. HE) hall-ne.1.

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-methylimidazol-2-vl)]methyl-6phenyl-2-phenylmethyl-hexanamide

a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-13-4 

Cbz-(L)-valinal (1.0 g, 3.9 mmol) and pyruvaldehyde (4.3 mmol, 40% in  $H_2O$ ) were dissolved in methanol (10 mL) and 15 chilled in an ice bath. Concentrated aqueous ammonia (2 mL) was added and the reaction mixture was stirred at 20°C overnight. The solvent was removed in vacuo and the residue dissolved in 5% HCl (50, mL) and extracted with ethyl acetate (3x20 mL). The aqueous layer was basified to pH 10 with solid Na<sub>2</sub>CO<sub>3</sub>. A tan solid (463 mg) precipitated. The solid was purified by flash chromatography (silica, 2%-3%

methanol/dichloromethane) to yield the title compound as a white solid (180 mg, 16%). mp 163-164°C; NMR (CDCl3)  $\delta$  7.45-7.35 (5H, m), 6.60 (1H, s), 6.00 (1H, d, J=4 Hz), 5.05 (2H,

25 q, J=4 Hz), 4.40 (1H, t, J=4 Hz), 2:45-2:30\*(1H, m), 2:20 (3H, s), 0.95 (3H, d, J=4 Hz), 0.80 (3H, d, J=4 Hz); MS m/e 575.4 (2M+H)+, 288.0 [M+H]+. by 6-5 years q=0-5 years ( 1 The second of the second was the contract of the second of

b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino 4-t-1 % 30 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-methylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1(b)-1(c), except using (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4-t-- butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid and -35 the compound of Example 23(a), the title compound was prepared. NMR(CDCl<sub>3</sub>) & 7.37-6.90 (10H, m), 6.45 (1H, s), 6.38 (1H, d, J=3 Hz), 4.75 (1H, d, J=5 Hz), 4.40 (1H, t, J=5 Hz), 3.95 (1H, q, J=4:Hz), 3.72-3.68 (1H, m); 2.90-2.70 (4H,

m), 2.60-2.48 (1H, m), 2.45-2.30 (1H, m), 2.17 (3H, s), 1.90-1.80 (1H, m), 1.75-1.62 (1H, m), 1.40 (9H, s), 0.95 (9H, s), 0.75 (6H, t, J=3 Hz), 0.10 (6H, d, J=2 Hz).

isopropyl-1'-(4-methylimidazol-2-yl)]methyl-6-phenyl-2phenylmethyl-hexanamide

The compound of Example 23(b), the title compound was prepared. NMR(CDCl3) & 7.38-7.00 (10H, m), 6.52 (1H, s), 1.52 (1H, d, J=5.Hz), 4.42 (1H, t, J=4.Hz), 3.72-3.55 (2H, m), 2.95-2.65 (5H, m), 2.35-2.20 (1H, m), 2.18 (3H, s), 1.75 (2H, br s), 1.42 (9H, s), 0.75 (6H, d, J=3.Hz); MS m/e 549.2 [M+H]<sup>+</sup>.

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#### Example 24

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl) amino-4hydroxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-220 yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4trifluoromethylimidazol-2-yl) methane.

(m iii) or Sodium acetate trihydrate (5.35 g, 2.2 eq) was dissolved 25 in water (16 mL) and 1,1 dibromotrifluoroacetone (5.31 g, 1.1 eq) was added. The solution was stirred for 30 min at 90°C. The solution was cooled to 0°C and poured into a 0°C solution of Cbz-Valinal (4.22 g, 1.0 eq) in anhydrous methanol (80 mL). Concentrated ammonium hydroxide (22 mL) was added and 30 the mixture stirred overnight at room temperature. The solvents were evaporated to give a white precipitate which was covered with 150 mL of water. The suspension was filtered and the solid washed twice with water. The white solid was dissolved in ethyl acetate, dried over sodium sulfate, 35 filtered, and evaporated to a white solid (5.24 g, 86%).

1HNNMR (CD3OD) & 7.45 (1H, s), 7.40-7.20 (5H, m), 5.05 (2H, q, J=4 Hz), 4.50 (1H, d, J=4 Hz), 2.38-2.10 (1H, m), 1.00 (3H, mc) of d, J=4 Hz), 0.80 (3H, d, J=4 Hz), 13CNMR (CD3OD, 1H-decoupled)

20

δ 18.9, 19.4, 67, 117 (q, J=3 Hz), 123.2 (q,  $\overline{J}$ =266 Hz), 128.7, 129.3, 133 (q, J=39 Hz), 138.0, 151.7, MS m/e 342.0 [M+H]<sup>+</sup>.

b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyl-dimethylsiloxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-2-yl)] methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 1(b)-1(c), except using the compound of Example 24(a) and (2R, 4S, 5S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid, the title compound was prepared.

NMR(CDCl<sub>3</sub>) & 7.35-6.95 (11 H, m), 6.50 (1H, d, J=4 Hz), 4.75 (1H, d, J=6 Hz), 4.25 (1H, t, J=4 Hz), 3.95 (1H, q, J=4 Hz), 3.80-3.68 (1H, m), 2.90-2.40 (5H, m), 1.80-1.60 (2H, m), 1.35 (9H, s), 0.90 (9H, s), 0.80 (3H, d, J=3 Hz), 0.70 (3H, d, J=3 Hz), 0.05 (6H, d, J=2 Hz).

c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 9(d), except using the compound of Example 24(b), the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 7.35 (1H, s), 7.25-6.90 (10H, m), 4.53 (1H, d, J=5 Hz), 3.68 (1H, t, J=4 Hz), 3.52 (1H, d, J=6 Hz), 2.90-2.55 (5H, m), 2.10-1.95 (1H, m), 1.85-1.70 (1H, m), 1.65-1.50 (1H, m), 1.40-1.25 (9H, m), 0.90 (3H, d, J=4 Hz), 0.65 (3H, d, J=4 Hz); MS m/e 603.2 [M+H] +, 529.2, 503.2.

# Example (25) Land (5% xo) 10 days to know as Equivarianone ; ... (day

- Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-methyl-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethyl-hexanamide
  - a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(imidazol-2-yl)methane

Following the procedure of Example 1(a), except substituting N-methyl-Cbz-(L)-valinal for Cbz-(L)-valinal, the title compound was prepared. NMR(CDCl3) 8 7.45-7.30 (5H,

m), 6.90 (2H, s), 5.12 (2H, s), 4.60 (1H, d, J=6 Hz), 2.95 (3H, s), 2.70-2.53 (1H, m), 1.02 (3H, d, J=3 Hz), 0.85 (3H, d, J=3 Hz).

5.1 b) (1S)-1-methylamino-1-isopropyl-1-(imidazol-2-yl)methane Following the procedure of Example 1(b), except using the compound of Example 25(a), the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 6.95 (2H, s), 3.52 (1H, d, J=3 Hz), 2.30 (3H, s), 2.10-1.90 (1H, m), 0.98 (3H, d, J=3 Hz), 0.82 (3H, d, J=3 Hz).

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- (a) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl) amino-4-t
  butyldimethylsiloxy-N-methyl-N-(1'-isopropyl-1'-imidazol-2
  yl) methyl-6-phenyl-2-phenylmethyl-hexanamide
- Following the procedure of Example 1(c), except using the compound of Example 25(b), the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 7.40-6.72 (12H, m), 4.82 (1H, d, J=5 Hz), 3.95 (1H, q, J=4 Hz), 3.82-3.75 (1H, m), 2.95-2.70 (5H, m), 2.51 (2H, s), 2.50-2.38 (1H, m), 2.08 (1H, s), 1.87-1.68 (2H, m), 1.38 (9H, s), 0.95 (9H, s), 0.88 (3H, d, J=3 Hz), 0.75:(3H, d, J=3 Hz), 0.05 (6H, d, J=7 Hz).
- (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-Nleader to methyl-N-(1\*-isopropyl-1\*-imidazol-2-yl) methyl-6-phenyl-2v25 phenylmethyl-hexanamide

have producted that interpretability there is to be a finisher to be a

Following the procedure of Example 9(d), except using the compound of Example 28(c), the title compound was prepared. NMR(CDCl<sub>3</sub>) & 7.35-6.82 (12H, m), 4.90-4.72 (1H, m), 3.70-3.00 (2H, m), 2.92-2.50 (8H, m), 1.90-1.60 (2H, m), 30 1.40-1.30 (9H, m), 0.95-0.70 (6H, m).

MS m/e 549.2 [M+H]<sup>+</sup>.

### was earlyge risk theme . Example 26 to rear a

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-f1'-isopropyl-1'-(4-carbomethoxyimidazol-2yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

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a) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4- (5- trimethoxymethylimidazol-2-yl)methane:

Sodium methoxide (8 mL, 25% in methanol, 37.5 mmol) was added to a solution of the compound of Example 27(a) (640 mg, 1.88 mmol) in anhydrous methanol (10 mL). The resulting mixture was heated at 55°C overnight, cooled, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and H<sub>2</sub>O, and the organic extract was dried over Na<sub>2</sub>CO<sub>3</sub>. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 2% methanol/dichloromethane) to afford the title compound (545 mg, 77%). NMR(CDCl<sub>3</sub>) & 7.40-7.20 (5H, m), 6.98 (1H, br s), 5.90 (1H, br s), 5.08 (2H, s), 4.50 (1H, br s), 3.15 (9H, s), 2.00 (1H, m (br)), 1.00-0.80 (6H, m); MS m/e 378.2 [M+H]<sup>+</sup>, 346, 332, 271, 195.

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b) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4- carbomethoxyimidazol-2-yl)methane

A solution of the compound of Example 26(a): (540 mg) in 1:1 methanol/aqueous HCl (10 mL) was stirred at room temperature for 2 h, and concentrated under reduced pressure. The residue was partitioned between aqueous Na<sub>2</sub>CO<sub>3</sub> and dichloromethane, and the organic extract was dried over Na<sub>2</sub>CO<sub>3</sub> and concentrated in vacuo to afford the title compound (470 mg, 75%). NMR(CDCl<sub>3</sub>) & 7.55 (1H, br(s), 7.35 (5H, s), 5.90-5.65 (1H, m), 5.10 (2H, t, J=4 Hz), 4.60-4.42 (1H, m), 3.88 (3H, s), 2.40 (1H, br s), 1.00-0.80 (6H, m); MS m/e 332.2 [M+H]\*.

30 c) (1S)-1-amino-1-isopropyl-1-(4-carbomethoxyimidazol-2-2 yl)methane

Following the procedure of Example 1(b), except using the compound of Example 26(b), the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 7.62 (1H, s), 3.97 (1H, d, J=4 Hz),

11) 3 Med 30 (10) 31, 21, 5 (15)

35 3.82 (3H, s), 2.27-2.05 (1H, m), 0.95-0.75 (6H, m).

EAN (ES ), 1 (F 11.9) (S) (E S) and 1 for the special of

e) (2R, 4S, 5S, 1:S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N[1'-isopropyl-1'-(4-carbomethoxyimidazol-2-yl)] methyl-6phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 9(d), except using the compound of Example 26(d), the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 7.40-6.80 (12H, m), 4.90 (1H, d, J=5 2.68 (5H, m), 2.45-2.30 (1H, m), 1.80-1.60 (2H, m), 1.40 (9H, M), 2.62 (S), 00.72 (6H, d, J=40Hz); MS m/e 593.2 [M+H]+, 537.2, 519.2, MS 62493.2, 475.2.3.4

#### Example 27

25 1) Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl) amino-4hydroxy-N-[1'-isopropyl-1'-(4-methylcarbonylimidazol-2yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

The state of the property of the contract of the state of

(15)-1-carbobenzyloxyamino-1-isopropyl-1-(4-)

it is in a The compound of Example 26(b) (0.314.g; 1.0 eq) was attributed in anhydrous toluene at 78°C under an argon atmosphere. Diisobutylaluminum hydride (3.8 mL, 1.0M in 62 has richexanes, 4.0 eq) was added and the solution stirred at -78°C 2635 for 1 h. The reaction was quenched with methanol (0.2 mL, 1.0 mL, 1.0 eq). The solution was then diluted with Rochelles salt solution (sat.) and stirred for 1 h. The solution was extracted with dichloromethane twice and the combined organic

extracts were washed successively with saturated aqueous

Rochelles salt and brine. The organic layer was dried over

magnesium sulfate, filtered, and evaporated to give the title

compound as a white solid: (0.27 g/194%) polyMR(CDCl3) & 7.25

5 (5H, s), 6.69 (1H, s), 6.14 (1H, d), 5.01 (2H, dd), 4.52 (2H, s), 4.37(1H, t), 2.19 (1H, m), 0.92 (3H, d), 0.73 (3H, d); MS

m/e 304.0 [M+H]+...

- b) (18)-1-carbobenzyloxyamino-1-isopropyl-1-(4-02.1
  - 10 formylimidazol-2-yl)methane( R ( ) ,b ,R3), Of ,0 , (SR 0)

The compound of Example 27(a) (0.11 g, 1.0 eq) was stirred in anhydrous dichloromethane at room temperature under an inert argon atmosphere. Manganese dioxide! (0.126 g, 4.0 eq) was added and the mixture was stirred at room temperature overnight. After 16 h and additional 2.0 eq of manganese dioxide was added. The reaction was complete by TLC after 2 h. The mixture was filtered through a pad of Celite® and the filter cake was washed with dichloromethane. The organic solvent was removed in vacuo (to give the title compound as a white solid (0.075 g, 69%).) NMR(CDCl3) & 9.57 (1H, s), 7.54 (1H, s), 7.12 (5H, s), 6.43 (1H, d), 4.96 (2H, d), 4.43 (1H, t), 2.08 (1H, m), 0.91 (3H, d), 0.62 (3H, t);

c) (1S,1'RS)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'-hydroxyethyl)imidazol-2-yl)methane.

 $MS m/e 302.0 [M+H]^+$ .

The compound of Example 27(b) (0.1 g, 1.0 eq) was stirred in a 3:1 ether/THF mixture at 0°C under an argon atmosphere. Methyl magnesium bromide (0.47 mL, 3.0M in THF, 4.0 eq) was added and allowed to stir at 0°C for 1.5 h. The solution was diluted with 5% aqueous HCl and made basic with solid sodium carbonate. The solution was extracted with ethyl acetate three times and the combined organic extracts were dried over sodium carbonate, filtered, and evaporated to a white solid (0.1 g, 95%). NMR(CDCl3) & 7.19 (5H,s), 6.59 (1H, s), 6.42 (1H, d), 4.92 (2H, dd), 4.73 (1H, m), 2.09 (1H, m), 1.37 (3H, d), 0.82 (3H, d), 0.66 (3H, d).

d) (1S, 1'RS)-1-amino-1-isopropyl-1-(4-(1'-hydroxyethyl)imidazol-2-yl)methane.

5f.d), 0.84 (3H, d), 0.67 (3H, d).

stirred in anhydrous methanol with 10% Pd on activated carbon (0.020 g). Hydrogen gas was bubbled through the solution via balloon for 1 h and the reaction was maintained under a hydrogen atmosphere for 3 h. The mixture was filtered through a pad of Celite® and the filter cake washed with methanol. The methanol was evaporated to give the title compound as a white solid (0.05 g, 87%). NMR (CDCl3) & 6.63 (1H, s), 44.72 (1H, dd), 3.61 (1H, d), 1.92 (1H, m), 1.49 (3H,

2- 7 e) (2R, 4S, 5S, 1'S, 1'RS) -5-(t-butoxycarbonyl) amino-4-t-

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butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-(1''-hydroxyethyl)imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

To a solution of (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4t-butyldimethylsiloxy-6-phenyl-2-phenylmethylhexanoic acid (0.131-g,(1.0-eq) in anhydrous dimethylformamide, the

20 compound of Example 27(d) (50 mg, 1.1 eq), BOP reagent (0.11 g, 1.0 eq), and triethylamine (0.04 mL, 1.0 eq) were start dadded. The solution was stirred at room temperature for

4. 30 16 h. The solution was diluted with water and extracted three and stimes with dichloromethane. The combined organic extracts

over magnesium sulfate, filtered, and evaporated to give a white foam. In the foam was chromatographed (silica, 4%

of the intermediate of the state compound as a white foam (0:11.g, 65%). NMR(CDCl3) & 7.31-6.54 (12H, m),

0. 30 (4.72 (1H, d), 4.48 (2H, d), 3.82 (1H, q), 3.61 (1H, m), 2.81-(C.7 , 4.2.3 (6H, m), 01.65 (3H, m), 1.48 (3H, d), 1.22 (9H, s), 0.89

0v.0 (9H,00s), 0.70 (3H, d), 00.61 (3H, d), 00.06 (6H, s); MS m/e 693.4 [M+H] 1.0041 S.0020 (3H, d) 0.00 (3H, d), 00.06 (3H, s);

∴ 25°

f) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t- ( butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

The compound of Example 27(e) (45 mg, 1.0 eq) was stirred in dry dichloromethane under an inért argon atmosphere. Manganese dioxide (23 mg, 4.0 eq) was added and the mixture was stirred at room temperature for 16th. An additional 2.0 eq of manganese dioxide was added and the reaction was complete by TLC after 2.5 h. The mixture was filtered through a pad of Celite® and the filter cake was washed with dichloromethane. The organic solvent was evaporated to give the title compound as a white solid (0.038 g, 85%). NMR(CDCl<sub>3</sub>)  $\delta$  7.49-6.76 (11H, m), 6.30 (1H, br d), 4.71 (2H, m), 3.86 (1H, q), 3.61 (1H, dd), 2.77-2.41 · 15 · (5H, m), 2.31 (3H, s), 1.58 (2H, m), 1.20 (9H, s), 0.83 (9H, s), 0.69 (6H, dd), 0.04 (6H,d); MS m/e 691.4 [M+H]+.

g) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1'-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-

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The compound of Example 27(f) (38 mg, 1.0 eq) was stirred in anhydrous THF under an argon atmosphere at room temperature. Tetrabutyl ammonium fluoride (0.33 mL, 1.0M in THF, 6.0 eq) was added and the solution stirred for 16 h. The solution was diluted with water and extracted three times with dichloromethane. The combined organic extracts were washed with water and evaporated to as white solid. The solid was covered with diethyl ether, decanted twice, and dried to Ogive the title compound as a white solid (25cmg #579%).

30 NMR (CDCl<sub>3</sub>) 8 7.14 (5H, m), 6.86 (5H, m), 5.14 (1H, d), 4.42 (1H, d), 3:58 (1H, q), 3.45 (1H, d), 2.80-2.50 (5H, m), 1.91 (1H, m), 1.63 (2H, m), 1.26 (9H, s) ((rotamer observed), 0.70 (3H, d), 0.57 (3H, d); MS m/e 577.2 [M+H]+.

### Example 28

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-5 yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

price a) (1S, 1'RS)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'patients hydroxy-2'-methyl) propylimidazol-2-yl) methane.

and isopropylimagnesium bromide (1.024 mL, 2.0M solution, 4.0 eq)

in place of methyl magnesium bromide, to yield a crude

product. The crude product was chromatographed (silica, 4%

methanol/dichloromethane) to yield the title compound as a

white solid (0.155 g , 88%) NMR(CDCl3) & 7.19 (5H, m), 6.58

15 (1H, s), 4.91 (2H, m), 4.38 (1H, q), 4.20 (1H, dd), 2.11 (1H,

m), 1.83 (1H, m), 0.72 (12H, m); Ms m/e 346.2 [M+H]+; 328.2,

279.0; 254.0, 205.0, 177.0, 149.0, 118.0.

i(a) (15,1'RS)-1-amino-1-isopropyl-1-(4-(1'-hydroxy-2'-b)20 g methyl) propylimidazol-2-yl) methane

3.7 0 ((3.3) Following the procedure of Example 27(d), using the compound tof Example 31(a), the title compound was prepared as abwhite foam (96 mg, (100%). NMR(CDCl<sub>3</sub>) δ (6.65 (1H, s), 4.21c(1H, rd), (3.90 (1H, s), 2.22 (1H, m), 1.94 (1H, m), 0.93 ch 25 l) (6H, m), 0.64 (6H, m); MS m/e 302.0 [M+H]<sup>+</sup>. (3.4)

the compound of Example 31(b) (96 mg, 1.1 eq), substituting dimethyl formamide as the solvent instead of dichloromethane, t and purifying the product by chromatography, the title

35 compound was prepared (168 g, 57%). NMR (CDCl<sub>3</sub>) δ:7.22-6.81 =(11H, m)/p 6.62.(1H, dd)/p 4.71 (1H, dd), 4.53 (1H, t), 4:19 - and him (1H, d)/p 3.82 (1H, q)/p 3.58 (1H, dd)/p 2.71-2.30 (5H, m), 2.03 - and (1H, m)/p 1.70 (1H, m)/p 1.57 (1H, m)/p 1.14 (9H, s)/p 0.91 (3H, d), 0.88 (9H, s), 0.78 (3H, d), 0.67 (3H, d), 0.59 (3H, d), 0.03 6H, d); MS m/e 721.4 [M+H]+. The second of the contract of the second of

d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl) ]methyl-6-phenyl-2-phenylmethyl-hexanamide Following the procedure of Example 27(f) Pexcept using the compound of 31(c) (168 mg, 1.0 eq) and chromatographing the crude product (silica, 13%) methanol/dichloromethane) the title compound was prepared as a white solid (132 mg, 79%). NMR (CDCl<sub>3</sub>) & 7.20-6.76 (11H, m) .....5.05 (1H, 5br<sub>5</sub>m), 3.88 (1H, q), 3.61 7 m), 3.19 (1H, m), 2:80-2.46 (5H, m), 62.22 (1H, m), 2.07 (1H, m), 1.63 (1H, m), 1.15 (16H, dm) 7 01891 (9H, s), 30.74 (6H, m), 0.08 (6H, d); MS m/e 719.4 [M+H]+44 (f) LARS TO THE MEDITINE WILL AT THE SE

(1) is. 2.

e) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'isopropyl-1'-(4-isopropylcarbonylimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 27(g), except using the compound of Example 31(d) (132 mg), the title compound 20 was prepared as a white foam (90 mg, 81%) with NMR (CDCl3) & 7.48 (1H, s), 7.11 (5H, m), 6.82 (5H, m), 5.29 (1H, ad), 64.46 (1H, m), 3.54 (1H, q), 3.48 (1H, m), 3.148 (1H, m), 2.74-2.44 (5H, (1.0) ((m), 1.90 (1H, m), 1.61 (2H, m), 1.28 (9H, ts) ((rotamers observed), 1.13 (6H, m), 0.69 (3H, d), 0.48 (3H, d); MS m/e 605.2 [M+H]+.

# Example 29 / le (videml) to

The second of the state of the control of the second of th

- Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-phenylcarbonyl-imidazol-2yl) |methyl-6-phenyl-2-phenylmethyl-hexanamide(moo) | 1 n. b. a Der eine an ibimmund ligitabitele
- a) (1S,1'RS)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1'hydroxy) benzylimidazol-2-yl) methane

Following the procedure of Example 27(c)/ except substituting phenylmagnesium bromide (0.45 mL, 3.0M solution, 4.0 eq) for methyl magnesium bromide, and chromatographing

the crude product (silica, 3% methanol/dichloromethane) the title compound was prepared as a white solid (175 mg, 96%).

NMR(CDCl<sub>3</sub>) & 7.26 (1H, d), 7.11 (10H, m), 6.39 (1H, dd), 6.08

(1H, d), 5.63 (1H, d), 4.82 (2H, m), 4.29 (1H, m), 2.01 (1H, 5 m), 0.76 (3H, m), 0.59 (3H, d).

(m NEED) ((1S,1:RS)-1-amino-1-isopropyl-1-(4-(1:-hydroxy)benzyl-(m NEX)imidazol-2-yl)methane(NEE) (AB) (AB) (AB) (REALTH (NEED) (NEED)

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the compound of Example 29(a) (98 mg) the title compound was prepared as a tacky white foam (65 mg, 98%).

c) (2R, 4S, 5S, 1'S, 1''RS) -5-(t-butoxycarbonyl) amino-4-tmin ubutyldimethylsiloxy-N-[1'-isopropyl-1'-(4-(1''- ))]

O'Control in

hexanamide hexanamide

Following the procedure of Example 27(e), except using the compound of Example 29(b) (0.065 g, 1.1 eq), and chromatographing the crude product (2% methanol/

20 dichloromethane) the title compound was prepared as a white brus solid (109 mg, 55%). NMR(CDCl<sub>3</sub>) & 7.48-6.79 (16H, m), 4.77

(1H, m), 2.15; (1H, m), (1.94 (1H, m), 1.75 (1H, m), 1.56 (1H, m), 1.21 (9H, s) (rotamers observed), 0.86 (9H, s), 0.68 (6H, 25 dd), 0.07 (6H, s); MS m/e 755.4 [M+H]+.

The Capabalifican (Cinnerasus co. acts) - 2- CH (CE (CI CH)) (C

d):(2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t-butyl-dimethylsiloxy-N-[1!-isopropyl-1!-(4-phenylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
ph30.quipt in Following the procedure Example 27(f), exceptousing the
cd (compound of Example 29(c) (109 mg, 1.0 eq), the title

compound was (prepared as) a white solid (80 mg, 74%).

NMR (CDC13) δ 7.49-6.84; (17H, m), 3.88 (1H, q), 3.63 (1H, t),

(id) 08 2.87-2.49; (6H, m), 2.11 (2H, m), 1.64 (1H, m), 1.11; (9H, s),

(iii) 08 (9H, s), 0.71; (6H, dd), 0.06; (6H, d); MS m/e 753.4;

(iii) (M+H)+.33.3 (6 JE 6.3.3); (2.3.3); (2.3.3); (2.3.3);

(b) 310b)

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e) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-phenylcarbonylimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 27(g) hexcept using

the compound of Example 29(d) (80 mg/s 1.0 eq), the title compound was prepared as a white solid (45 mg , 74%).

NMR(CDCl<sub>3</sub>) δ 7.84-6.77 (16H, m), 4.48-(1H, d), 3.59 (1H, m), 3.42 (1H, m), 2.80-2.54 (5H, m), 1.99 (1H, m), 1.63 (2H, m), 1.26 (9H, s) (rotamers observed), 0.73 (3H, d), 0.59 (3H, d); 10 MS m/e 639.2 [M+H]<sup>+</sup>.

#### Example 30

property of the four of the property

(2年, #8, 35, 37, 31, 14, 1235)

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4
1 1015 hydroxy-N-[1'-isopropyl-1'-(4-formylimidazol-2-yl)]methyl-6
phenyl-2-phenylmethyl-hexanamide

a) (1S,1'RS)-1-amino-1-isopropyl-1-(4-(hydroxy) methyl-imidazol-2-yl) methane. Or a state on a pathograph amount

with a normal of the Comment of the writing of the grade allow

Following the procedure of Example 27(d), except using the compound of Example 27(a) (90 mg), the titled compound was prepared (50 mg, 100%). NMR(CDCl<sub>3</sub>) & 6.85((1H, s), 4.62 (2H, s), 3.85 (1H, d, J=4 Hz), 2.20-2.05 (1H, m), 0.88 (6H, d, J=5 Hz).

25 (2.2 ). 13 (3.4 ). (8 (16) Vd.0 , 55

b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-'(4-(hydroxy) methyl-imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 27(é) ym except using 30: the compound of Example 30(a) (50 mg), and chromatographing the crude product (silica, 2% methanol/dichloromethane) the title compound was prepared (130 mg, 65%). NMR (CDCl3) 8

7.30-6.95 (11H, m), 4.82 (1H, d), 4.50-4.60 (1H, m), 4.40 (1H, d), 3.90-4.00 (1H, m), 3.60-3.68 (1H) m), 2.45-2.80 (5H, s), 2.20-2.30 (1H, m), 1.75-1.85 (1H, m), 1.60-1.70 (1H, m), 1.30 (9H, s), 0.95 (9H, s), 0.75 (3H, d), 0.62 (3H, d), 0.05 (6H, d).

(rotamers).

- c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-tbutyldimethylsiloxy-N-[1'-isopropyl-1'-(4-formylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
- 5 the compound of Example 30(b) (50 mg), the title compound was prepared (20 mg, 40%). NMR(CDCl<sub>3</sub>) δ 9.80(0.5H, s), 9.64
  (0.5H, s), 7.50-6.90 (11H, m), 6.52-6.42 (1H, m), 4.88-4.70 (2H, m), 4.42-4.32 (1H, m), 4.02-3.93 (1H, m), 3.78-3.71 (1H, m), 2.90-2.40 (5H, m), 2.30-2.19 (1H, m), 1.87-1.62 (2H, m), 1.45 (9H, s), 0.95 (9H, s), 0.87-0.72 (6H, m), 0.05 (6H, m)
  - d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'isopropyl-1'-(4-formylimidazol-2-yl)]methyl-6-phenyl-2phenylmethyl-hexanamide (6,100111)

Following the procedure of Example 27(g), except using the compound of Example 30(c) (20 mg), the title compound was prepared (12 mg, 71%). NMR(CD3OD) & 9.60 (1H, s), 7.65 (1H, s), 7.20-6.90 (10H, m), 4.52 (1H, d), 3.60 (1H, m), 3.45 (1H, d), 2.80-2.45 (5H, m), 2.00-1.88 (1H, m), 1.75-1.65 (1H, m), (1.62-1.45)(1H, m), 1.27 (9H, s), 0.82 (3H, d), 0.62 (3H, d); MS m/e 563.4, 242.2, 204.8:

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# Example 31

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-(hydroxymethyl)-imidazol-2yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

193.303 (a) Following the procedure of Example 27(g), except using the compound of Example 30(b) (40 mg), the title compound was prepared (20 mg). NMR(CD3OD) δ 7.27-6.92 (10H, s), 6.72 (1H, compound was prepared (20 mg). NMR(CD3OD) δ 7.27-6.92 (10H, s), 6.72 (1H, compound was prepared (20 mg). NMR(CD3OD) δ 7.27-6.92 (10H, s), 6.72 (1H, s), 6.72 (1H, m), 3.48 (1H, d), 2.82-2.50 (5H, m), 2.03-1.92 (1H, m), 1.78-1.67 (1H, m), 1.63-1.49 (1H, 35.0 m), 1.28 (9H, s), 0.80 (3H, d), 0.65 (3H, d); MS m/e 565.4.

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Preparation of (2R.4S.5S.1'S)-5-((tetrahydrothiopyran-4yl)oxycarbonyl)amino-4-hydroxy-N-(141-isopropyl-1'-imidazol-2sta 5 vl)méthyl-6-phenyl-2-phenylmethyl-hexanamide mon oda a nxeprited (20 mg, 10%). Reference & S. t. e. t., e. . . .

Following the procedures of Example 14 (a)-14 (c), except using 4-hydroxytetrahydrothiopyran in place of 2benzyloxyethanol, the title compound was prepared. Analytical data for the intermediates of this synthesis were: ing in leading (1911)

a) (tetrahydrothiopyran-4-yl)-(4-nitro)phenylcarbonate. NMR (CDCl<sub>3</sub>) δ 8.26 (1H, s) % 8.22 (1H, s) % 27.38 (1H, s) , 7.33 (1H, s), 4.79 (1H, m), 2.90-2.75% (2H, m), 2.70-2.52 (2H, m), 2.31-2.16 (2H, m), 2.10-1.90 (2H, m) the - Lydening to step collecting the process to of them of the

b) (2R,4S,5S,1'S)-5-((tetrahydrothiopyran-4-yl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethyl-hexanamide. NMR (CD3OD) 8 7.12-6.65 20 (10H, m), 6.64 (2H, s), 5.60 (1H; d), 4.362(2H, 2m), 3.58 (1H,

(3H, m), 1.93-1.74 (3H, m), 1.70-1.40 (4H, m), 0.61 (3H, Ed), 0.50 (3H, d).

#### Example 33

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Preparation of (2R.4S.5S.1'S)-5-((tetrahydro-4H-pyran-4vl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

- 20.30 Following the procedures of Example 14(a)-14(c), except using 4-hydroxytetrahydro-4H-pyran in place of 2-343 3.5 m & 2.7 benzyloxyethanol, the title compound was prepared. Analytical data for the intermediates of this synthesis were: organization in the first of the transfer of the country and the country are taken
  - 35 a) (tetrahydro-4H-pyran-4-yl)-(4-nitro)phenylcarbonate.... NMR (CDCl<sub>3</sub>)  $\delta$  8.32 (1H, s), 8.28 (1H, s), 7.41 (1H, s), 7.38 (1H, s), 5.00 (1H, m), 4.05-2.90 (2H, m), 3.68-3.49 (2H, m), 2.17-2.00 (2H, m), 1.95-1.75 (2H, m).

```
b) (2R, 4S, 5S, 1'S)-5-((tetrahydro-4H-pyran-4-yl) oxycarbonyl)-
amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-
phenyl-2-phenylmethyl-hexanamide. NMR(CD<sub>3</sub>OD) δ 7.16-6.89

(10H, m), 6.79 (2H, s), 4.54 (2H, m), 3.82-3.70 (2H, m),
3.69-3.62 (1H, m), 3.50-3.46 (1H, m), 3.45-3.35 (2H, m),
(2.79-2.65 (4H, m), 2.64-2.45 (3H, m), 2.00 (1H, m), 1.82-1.62 (3H, m), 1.55-1.45 (2H, m), 1.37 (1H, m), 0.79 (3H, d), 0.63
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# to continue (per the continue of the continue of Example 34). The continue of the continue of

Preparation of (2R.4S.5S.1'S)-5-(4-picolinyloxy)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

The compound of Example 1(d) was dissolved in neat TFA.

(1) After 10 min the solution was concentrated to provide the

amine salt, \((2R,4S,5S,1!S)-5-amino-4-hydroxy-N-(1!-isopropyl-

20 1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

- introductifluoroacetate. (IThis amine salt (25 mg, 1 eq) was

from dissolved in DMF, and (4-picolinium-(p-nitro)phenyl carbonate

print depenitrophenylate (23 mg, 1)eq) and triethylamine (0.04 mL, 5

bard man eq) (were added. The mixture was stirred under Ar for 17 h.

1 . 1 25 (\* Water was added and the mixture was extracted with

dichloromethane. The organic extracts were concentrated and the residue was triturated with ether to yield the title compound (20 mg, 61%). (NMR(CD3OD) & 8.52 (2H, d), 7.10 (14H, m), 6.87 (2H, s), 5.07 (2H, dd), 4.61 (1H, d), 3.80 (1H, m), 30. 3.59 (1H, m), 2.77 (5H, m), 2.05 (1H, m), 1.83 (1H, m), 1.60

MS m/e570.5% [M+H]<sup>+</sup>.Inches that the tension of th

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er, e and hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

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a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-(4,4,4-trifluorobut-1-yl)-tetrahydrofuran-2-one-les

To a solution of lithium dilsopropyl amide (1.8 mL of a 5 1.5M solution, 2.2 eq) in tetrahydrofuran (10 mL) was added (5S, 1'S)-(1'-t-butoxycarbonylamino-2, -phényl) éthyltetrahydrofuran-2-one (0.50 g; 1.0 eq) in anhydrous THF (2 mL) at -78°C. After stirring for 15 min at (-78°C.) hexamethylphosphoramide (0.57 mL, 2.0 eq) was added to the solution. The solution was stirred for several min and 1,1,1-trifluoro-4-iodobutane (0.78 g, 2.0 eq) was added. After 2 h at -78°C, the reaction mixture was quenched with a 10% aqueous HCl and extracted with dichloromethane. organic extracts were combined and evaporated to a clear oil. The oil was chromatographed (silica, 2% methanol/si dichloromethane) to give the title compound as a white foam (0.248 g, 37%). NMR: (CDC13)  $\delta$  7.18 (5H, m), 4.57 (1H; d), 4.41 (1H , dd) , 3.95 (1H , q) , 2.82 (2H, d) , 12:55 (2H , m) , 2.49-1.49 (7H , m), 1.32 (9H , s); MS m/e 438.0 (M+Na)+.

b) (2R, 4S, 5S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethyl-siloxy-6-phenyl-2-(4, 4, 4-trifluorobut-1-yl) hexanoic acid

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Following the procedure of Example 12(b), except using the compound of Example 35(a) (245 mg), the title compound was prepared (215 mg, 67%). NMR(CDCl3) & 7.18 (5H; m), 4.70 (1H, d), 3.88 (1H, q), 3.69 (2H, m), 2.73 (1H, m), 2.38 (1H, m), 1.91 (2H, m), 1.45 (6H, m), 1.31 (9H, s) (rotamers observed), 0.90 (9H, s), 0.08 (6H, d); MS m/e548.2 [M+H]+.

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c) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-t-butyl-dimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-trifluorobut-1-yl)hexanamide

Following the procedure of Example 1(c), except using the compound of Example 35(b) (100 mg) and (1S)-1-imidazol-2-yl-35 2-methylpropylamine, the title compound was prepared (83 mg, 68%). NMR(CDCl<sub>3</sub>) δ 7.22 (5H, m), 7.03 (1H, d), 6.89 (2H, s), 4.72 (1H, d), 4.51 (1H, t), 3.91 (1H, q), 3.65 (1H, m), 2.78 (2H, d), 2.33 (2H, m), 1.82 (4H, m), 1.48 (4H, m), 1.36 (9H,

two singlets; rotamers present), 0.99 (9H, s), 0.91 (3H, d), 0.79 (3H, d), 0.07, (6H, d); MS m/e669.4 [M+H]+.

(2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-(1'-5-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-trifluorobut-1-yl)hexanamide

Following the procedure of Example 9(d), except using the compound of Example 35(c) (83 mg), the title compound was prepared (40 mg, 58%). NMR(CD3OD) & 7.19 (5H, m), 6.92 (2H, 10 m s), 4.61 (1H, d), 3.64 (1H, q), 3.48 (1H, m), 2.79 (2H, m), 2.49 (1H, m), 2.13 (4H, m), 1.60 (5H, m), 1.36 (9H, s), 0.90 (3H, d), 0.71 (3H, d); MS m/e555.2 [M+H]+.

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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-v1))methyl-hexanamide hydrochloride

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2010 a) 2-(1'-carbobenzyloxyamino-1'-isobutyl) methyl-imidazole

(1.00 Following the procedure of Example 1(a), except
substituting Cbz-isoleucinal (1.83 g) for Cbz-valinal, the
title compound was prepared (0.658 g, 31%). NMR(CDCl3) δ

6.96 (2H, s), 5.31 (1H, d), 4.48 (1H, dd), 2.15 (1H, m), 1.44

25 (9H, s), 1.172 (2H, m), 0.92 (3H, t), 0.82 (3H, d); MS

(DCI/NH3) m/e 254.2 [M+H]<sup>+</sup>.

b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-yl)) methyl-hexanamide hydrochloride

substituting the compound of Example 36(a) for (1'S)-1'-

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which carbobenzyloxyamino-1'-isopropyl-1'-(imidazo-2-yl)methane,

35 7:29-7:02 (10H, m), 6.89 (2H, s), 6.50 (1H, d), 4.81 (1H, m), 4.55 (1H, dd), 3.56 (1H, m), 2.69 (5H, m), 1.80 (1H, m), 1.59 (2H, m), 1.30 (9H, s), 1.17 (2H, m), 0.78 (3H, t), 0.63 (3H, dd); MS (DCI/NH3) m/e 549.7 [M+H]<sup>+</sup>.

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-((IRS)-1-hydroxyethyl)imidazol-2-yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide Therefore the expression of the expression of the endinglish

The t-butyldimethylsiloxy-protected alcohol from Example 30(e) (20 mg, 1.0 eq) was stirred in anhydrous THF under an argon atmosphere at room temperature. Tetrabutyl ammonium fluoride (0.33 mL of a 1.0M solution in THF, 6.0 eq) was added and the solution stirred for 16 h. The solution was diluted with water and extracted with dichloromethane. combined organic extracts were washed with water and evaporated to a white solid. The solid was covered with diethyl ether and decanted twice to give the title compound as a white solid. (0.012 g, 72%). A NMR (CDCl<sub>3</sub>)  $\delta$  7.22-6.84 (10H, m), 6.61 (1H, s); 5.42 (1H, d); 4.692(1H; m); 4.41 (1H, d), 3.58 (1H, m), 3.45 (1H, m), 2.78-2.40 (5H, m), 1.91 (1H, m), 1.59 (2H, m), 1.41 (3H, d), 1.26% (9H, s) 1 (rotamers: observed), 0.71 (3H, d), 0.59 (3H, d); MS m/e 579.2 [M+H]+. The second of medical political decides

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25 Preparation of (2R.4S.5S.1'S)-5-(1"1-dimethyl-2-") hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-1sopropyl-1'imidazol-2-vl)methvl-6-phenvl-2-phenvlmethvl-hexanamide on the second place and the second place of th

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a) 2-t-butyldimethylsiloxy-1,1-dimethylethyl-(4- 30 nitrophenyl) carbonate to out to a street to the street to

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A mixture containing bis (4-nitrophenyl) carbonate (0.996 g, 3.28 mmol); 2-t-butyldimethylsiloxy-1;1dimethylethanol (0.67 g, 1 eq) and 4-dimethylaminopyridine (0.4 g, 1 eq) in dichloromethane (50 mL) was stirred at room temperature for 5 d. The mixture was diluted with dichloromethane and washed successively with H2O and saturated aqueous NaCl, and dried over Na2CO345 The solvent was removed in vacuo, and the residue was purified by flash

chromatography (silica, 20% ethyl acetate/hexanes) to afford the title compound (35%). NMR(CDCl<sub>3</sub>) & 8.25 (2H, m), 7.35 (2H, m), 3.76 (2H, s), 1.53 (6H, s), 0.94 (9H, s), 0.09 (6H, s).

b) (2R, 4S, 5S, 1'S)-5-(2-t-butyldimethylsiloxy-1,1-dimethyl-ethoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

A solution of 2-t-butyldimethylsiloxy-1,1-dimethylethyl4-nitrophenyl carbonate (137 mg, 0.372 mmol), (2R,4S,5S,1'S)5-amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (102 mg, 0.186
mmol) and DMAP (45 mg, 0.372 mmol) in methylene choride was
stirred at 20°C under Ar for 24 h. The solution was washed
with aqueous Na<sub>2</sub>CO<sub>3</sub>, dried over solid Na<sub>2</sub>CO<sub>3</sub> and concentrated.
Flash chromatography (4\* methanol/dichloromethane) provided
the intermediate (2R,4S,5S,1'S)-5-(2-t-butyldimethylsiloxy1,1-dimethylethoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-

(1'-isopropyl-1'-(1-(2-t-butyldimethylsiloxy-1,120 dimethylethoxycarbonyl)imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide, which was dissolved in ether, washed with 10% NaOH, dried over Na<sub>2</sub>CO<sub>3</sub>, and concentrated to provide the title compound (110 mg, 78% overall). NMR(CDCl<sub>3</sub>) & 7.376.70 (13H, m), 6.39 (1H, d), 4.84 (1H, d), 4.55 (1H, t), 3.96
25 (1H, q), 3.69 (2H, s), 3.60-3.42 (2H, m), 2.94 (1H, s(br)),
2.85-2.44 (4H, m), 2.39 (1H, q), 1.90-1.60 (2H, m), 1.31 (6H,

d), 1.02-0.85 (18H, m), 0.83 (6H, t), 0.98 (12H, m).

c) (2R,4S,5S,1'S)-5-(1,1-dimethyl-2-hydroxyethoxy30 carbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

2. A mixture containing the compound of Example 38(b) (110
mg) and tetra-n-butylammonium fluoride (6 eq of 1M solution
in THF) under an argon atmosphere was allowed to stir at room
35 temperature overnight. The solution was diluted with
dichloromethane and washed with water, and the organic layer
was concentrated. The residue was purified by flash
chromatography (4% methanol/dichloromethane) to afford the

title compound (0.05 g, 66%). NMR (CDCl3; CD3OD) & 7.30-6.78 (12H, m), 4.42 (1H, d), 3.75-3.38 (4H, m), 2.97-2.50 (5H, m), 2.08 (1H, m), 1.70-1.56 (2H, m), 1.30 (6H, s), 0.90-0.55 (6H, dd).

## Example 39

Preparation of (2R.4S.5S.1'S)-5-(1:1-dimethyl-2-hydroxy-ethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide hydrochloride

A 1M solution of HCl in ether (63.5 mL) was added to a solution of the compound of Example 38(c) (35 mg, 0.064 mmol) in methanol (5 mL). The solvent was removed by rotary evaporation at 20°C, and the solid residue was triturated with ether and dried to afford the title compound as the hydrochloride salt (35 mg, 95%). NMR(CD<sub>3</sub>OD)  $\delta$  7.37-6.85 (12H, m), 4.56 (1H, d), 3.59 (1H, m), 3.48-3.33 (3H, m), 2.85-2.48 (6H, m), 2.04 (1H, septet), 1.72-1.49 (2H, m), 1.22 (6H, d), 0.88(3H, d), 0.61 (3H, dd).

# Example 40

Preparation of (2R.4S.5S.1'S)-5-(2-hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenyl-2-phenylmethylhexanamide

a) benzyloxyethyl-(4-nitro)phenylcarbonate

To a solution of 2-benzyloxyethanol (2.5 g, 16.4 mmol)

and bis(4-nitrophenyl)carbonate (5.0 g, 1 eq) in

dichloromethane (200 mL), N-methylmorpholine (1.81 mL, 1 eq)

was added. The resulting mixture was allowed to stir at room

temperature for 3 d. The reaction mixture was washed

successively with H2O and saturated aqueous NaCl and dried

over Na2SO4. The solvent was removed in vacuo, and the

residue was purified by flash chromatography (silica, 20%

ethyl acetate/hexanes) to afford the title compound (4.38 g,

4.49 (2H, t), 3.70 (2H, t).

b) (2R, 48, 38, 1.5) -5-(2-benryloxyethorgen-bonyl) amino-4-t
5 butyldimethylillary #-[1-isopropyl-1-48--(2-benzylogy-thorgen-bonyl-2-yl] benzylogy-thorgen-bonyl-2-yl] benzylogy-thorge

butyldiscription of (28,48,58,1-8)-3-emino-4-tbutyldiscription of (128,48,58,1-8)-3-emino-4-tbutyldiscription of (128,48,68,1-8)-3-emino-4-tbutyldiscription of (128,48,68,1-8)-3-emino-4-tbutyldiscription of (128,48,68,1-8)-3-emino-4-timidazol-2-yl) methylin (128,48,68,1-8)-3-emino-4-tdichloruscription of (128,48,68,1-8)-3-emino-4-tdichloruscription of (128,48,1-8)-3-emino-4-tdichloruscription of (128,48,1-8

benzylowethyl 4-nitrophenyl carbonate (150 mg, 2 eq) and 4-dimethylaminopyridine (60 mg, 2 eq) were added. The resulting mixture was allowed to stir at room temperature

overnight, and was diluted with dichlomenthane. The organic extract was washed successively with agreeous Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O<sub>4</sub>,

aqueous EngCD; and H2Q, and dried over EngCO3. The solvent was removed in vacuo, and the residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to

20 afford the title compound (180 mg, 82%). NMR (CDCl3) & 7.45-6.80 (22%, m), 6.62 (2H, d), 5.60 (1H, t), 5.06 (1H, d), 4.60 (2H, s), 4.52 (2H, s), 4.50 (2H, m), 4.31 (1H, m), 4.07 (2H, m), 3.80 (2H, t), 3.68 (1H, q), 3.57 (1H, q), 2.85 (1H, m), 2.77-2.41 (4H, m), 2.89 (1H, m), 1.90 (2H, m), 1.73 (1H, m),

25 0.95 (9H, s); 0.81 (6H, 5d), 0.11 (6H, d). -((vecologoroda ()-- g) od villentij prinjentij

c) (2R,4S,5S,1'S)-5-42-by-condensyl) amino-4-t-butyl-dimethylsiloxy 1-[1 dangersyl-1-E-2-benzyloxyethoxy-carbonyl) imidazol 2-yl) at hyl-6-phenyl 2-phenylmethyl-30' hexanamide

The compound of Example 40(b) (68 mg, 0.44 mmol) was stirred as a solution in mathemal (50 mg) with Pd(0) (10 mg) under 1 atm hydrogen for 12 h. The mixture was filtered, the solvent as a solution in mathemal the maxidue was purified by flash characteristics (1112, 44 mg, 744). IMR (CDCl3) & 7.36-6.72 (122, 30, 333 138, d), 4.80 (18, dd), 4.50-4.32 (28,

m), 4.07-3.52 (5H, m), 2.96-2.32 (6H, m), 1.98-1.85 (2H, m), 0.95 (9H, s), 0.90-0.75 (6H, dd), 0.05 (6H, d).

d) (2R, 4S, 5S, 1'S) -5-(2-hydroxyethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2and the phenylmethyl-hexanamide and franchische of exact agraph which

To a solution of the compound of of Example 40(c) in methanol, excess aqueous HCl (approx. 5 equiv.) was added. The resulting solution was stirred at room temperature 10 overnight, and concentrated under reduced pressure. residue was diluted with H2O, and made basic with aqueous The mixture was extracted with dichloromethane, and the combined organic extracts were dried over Na2CO3. solvent was removed in vacuo, and the residue was purified by flash chromatography to afford the title compound. NMR(CD3OD) 8 7.28-6.85 (12H, m), 4.55 (1H, d), 3.95 (1H, m), 3.73-3.40 (4H, m), 2.86-2.47 (5H, m), 1.99 (1H, m), 1.71 (1H, m), 1.22 (1H, m), 0.84 (3H, d), 0.62 (3H, d)

> ក ត្រាប់រីរី កែរ៉ូ ក្រុ<mark>ស្សែ</mark>ធារ៉ូត្រែក កែលពី។ Example 41 and the state of the

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Preparation of (2R, 4S, 5S, 1'S) -5-((1RS) -1-methy1 hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

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્ર(a) તથા 🖓 🤄 a) 2-t-butyldimethylsiloxy-1-methylethyl-(4-nitrophenyl)carbonate 

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A mixture containing bis (4-nitrophenyl) carbonate (3.20 g, 10.5 mmol), 2-t-butyldimethylsiloxy-1-methylethanol (2.0 g, 10.5 mmol) and 4-dimethylaminopyridine (1.30 g, 10.5 mmol) in dichloromethane (200 mL) was stirred at room temperature for 5 d. The mixture was then diluted with dichloromethane and washed successively with H2O and saturated aqueous NaCl and dried over Na2CO3. The solvent 35 was removed in vacuo, and the residue was purified by flash chromatography (silica, 10% ethyl, acetate/hexane) to, afford the title compound (88%). NMR(CDCl<sub>3</sub>)  $\delta$  8.28 (2H, m), 7.39

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ions (2H, m), 4.98 (1H, m), 3.75 (2H, d), 1.38 (3H, s), 0.92 (9H,
. Apriles . As) , O.11r. (6H, Is) . Halogue halita year on the
                     BURN OF A IN BURN WESTERN WILL
           (2R, 4S, 5S, 1'S) -5-(2-t-butyldimethylsiloxy-1-methyl-
                       ethoxycarbonyl)amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-
                        1'-imidazol-2-y1) methyl-6-phenyl-2-phenylmethyl-hexanamide
                   -> Following the procedure of Example 38(b), except
                        substituting the compound of Example 4(a) for 2-t-
  a; 6:.1; butyldimethylsiloxy-1,1-dimethylethyl-4-nitrophenyl
         2.10 paccarbonate, the title compound was prepared. NMR (CDCl3) δ
   State o os7.40-7.00 (10H/(m), 6.90 (1/2H/ms), 66.72 (1/2H/, s), 6.45 (1H,
         ar sardd), 74.92 3(1H, dd), 4.84-4.61 (2H, m), 4.10 (1H, m), 3.76
  bracks of (1H, m), 3.58: (1H, m), 2.92-2.73: (3H, m), 2.70-2.45 (3H, m),
    1.78 (2H, m), 1.22-1.08 (3H, m), 1.04-0.81 (24H, m), 0.17-
        5 15 10.09 (12H, m).
                            this bear will be as out our mile
       25: 0 1c) 2(2R, 4S, 5S, 1'S) -5-((1RS)-1-methyl-2-hydroxyethoxycarbonyl)-
          vices camino-4-hydroxy-N-(1!-isopropyl-1'-imidazol-2-yl)methyl-6-
                    phenyl-2-phenylmethyl-hexanamide
                                    Following the procedure of Example 38(c), except using
             20
                       the compound of Example 4(b), the title compound is prepared.
                     -NMR(CD_3OD) 8.7.15-6.68 (12H, m), 5.72-5.60 (1H, dd), 4.58
     -ty--: 8--- (1H, m) /- 4.38 - (1H, dd) / 3.406 \(1H, m) / 3.62 \(1H, m) / 3.41 \(1H,
      (5.65 \pm 0.03) \times (2.79 \pm 2.55) \times (5.67 \pm 0.03) \times (2.49) \times (1.92) 
             25 m), 1.08-0.98 (3H, dd), 0.69 (3H, dd), 0.58 (3H, dd).
          The properties against a by another only by the field of the
         -Lydding two of of of the tracking fine Example 42 for the tracking the
       (Come CS-10 16) field that the thirty of the constant
           # 1 Preparation of (2R.4S.5S.1'S)-5-(2-hydroxy-1-# )
        ad30 .cvclopentvloxycarbonyl)amino-4-hvdroxy-N-(1'-isopropyl-1'-
           badesimidazol-2-vl)methyl-6-phenyl-2-phenylmethylhexanamide
           has included adjoining matter and a section of
                   65a): (trans)-2-(t-butyldimethysiloxy)-cyclopentanol: 5
       cubized adl Toranmixture of t-butyldimethylsilyl chloride (5.08 g,
                        33.7 mmol) and imidazole (2.30 g, 33.7 mmol) in DMF (10 mL),
       to as assolution of trans-1,2-cyclopentanediol in DMF (4 mL) was
                        added. The reaction mixture was stirred overnight at 25°C.
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The reaction mixture was diluted with ice water and extracted

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with ether. The ether extract was washed with water and brine, dried over magnesium sulfate; filtered and the solvent removed in vacuo. The residue was purified by flash chromatography (silica, 9:1 hexane:ēthyldacetāte) to the title compound as an oil (3.44 g, 49%) modisayands 2

b) ((trans)-2-(t-butyldimethysiloxy)-cyclopentyl)-(4nitrophenyl) carbonate and compared a mildudimedia

To a solution of the compound of Example 42(a) (1.08 g, 5 mmol) and DMAP (0.611 g, 5 mmol) in dichloromethane (12 mL), bis (4-nitrophenyl) carbonate (1.52 g, 5 mmol) was added. The solution was stirred overnight at 25°C. The reaction mixture was diluted with dichloromethane (15 mL), and washed with water and brine. The organic extract was dried over magnesium sulfate, filtered, and the solvent was removed at reduced pressure. The residue was triturated with hexane:ethyl acetate (1:1) and filtered. The filtrate was evaporated to an oil and purified by flash chromatography (silica, 9:1 hexane:ethyl acetate) to yield the title compound as an oil (1.75 g, 92%).

c) 5-((trans)-2-t-butyldimethylsiloxy-cyclopentyloxy-carbonyl) amino-4-t-butyldimethysiloxy-N-[1'-isopropyl-1'-(1-(2-t-butyldimethysiloxy-cyclopentyloxycarbonyl)) imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide().

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A solution of 5-amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide (171 mg, 0.311 mmol), DMAP (76.1 mg, 0.623 mmol) and the compound of Example 42(b). (238 mg, 0.623 mmol) in dichloromethane (9 mL) was stirred overnight at 25°C. (The reaction mixture was diluted with dichloromethane, washed with water and saturated sodium bicarbonate solution, and dried with magnesium sulfate. The organic extract was filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (silica, 4:1 at hexane:ethyl acetate) to yield the title compound as an oil (150 mg, 47%).

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d) 5-((trans)-2-hydroxy-cyclopentyloxycarbonyl) amino-4hydroxy-N-[1'-isopropyl-1'-imidazol-2-yl]methyl-6-phenyl-2phenylmethyl-hexanamide

To a solution of the compound of Example 42(c) (150 mg, 0.145 mmol) in methanol (5 mL), 3N HCl (3 mL) was added. The solution was stirred overnight at 25°C. The methanol was evaporated in vacuo, and the residue was diluted with water and extracted with ether. The aqueous solution was neutralized with 5% sodium carbonate (~pH 7) and a solid precipitated. The solid was filtered, washed with water and dried in vacuo to yield the title compound (51.5 mg, 63%).

NMR(CD3OD, 400 MHz); 8,7.0-7.3 (m, 10H), 6.87 (s, 2H), 4.63

(in, 2H), 3.88 (m, 1H), 3.55 (d, 1H), 2.5-2.9 m, 5H), 1.4-2.1

11 (br, 9H), 0.88 (d, 3H), 0.71 (d, 3H); TLC Rf 0.27 (silica, 8% methanol/chloroform).

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Preparation of (2R.4S.5S.1'S)-5-(4-hydroxybutanoyl)amino-4-20 hydroxy-N-(1'-isopropyl-1'-imidazol-2-vl)methyl-6-phenyl-2phenylmethylhexanamide

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marily with the constitute of the Cinner

- a) t-butyldimethylsilyl 4-(t-butyldimethylsiloxy)-butanoate

  To a suspension of t-butyldimethylsilyl chloride (29.9

  25. \g, 198)mmol) in dry DMF (20 mL), 4-hydroxybutyric acid,

  8.2 in sodium salts (5.0 g, 397 mmol) and imidazole (27.0 \g, 0.397 mol); were added. The reaction mixture was stirred overnight

  at 25°C. The solvent was removed under reduced pressure and

  the residue was diluted with 10% aqueous citric acid (200

  30 mL). The residue was extracted with ether. The ether

  (3.5 solution was dried with magnesium sulfate, filtered and

  (3.5 solution was dried with magnesium sulfate, filtered and

  (3.5 solution was dried with magnesium sulfate, filtered and
  - (b) 4-t-butyldimethylsiloxy-butanoic acid (5.0 g) was addissolved in acetic acid:tetrahydrofuran:water (2:2:1, 50 mL) solution and stirred for 2.5 h. The solution was diluted with water and extracted with ether. The ether solution was

70. (iii (1) 7. 0-3. 3 (a) 30. 7. 35 (a) 30. 3. (b) 3. (c) 40 (a) 5. (c) 7. (c) 7. (c)

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dried with magnesium sulfate, filtered and evaporated to an oil. The oil was purified by flash chromatography (silica, hexane-ethyl acetate, 9:1) to yield the title compound as an oil (180 mg). a bure part of the mediation a of The state of the s

c) (2R, 4S, 5S, 1'S) -5-(4-t-butyldimethylsiloxy-butanoyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

A solution of (2R, 4S, 5S, 1'S) -5-amino-4-t- 136 36 in 100 butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (175 mg, 0.319 mmol), 4-tbutyldimethylsiloxy-butanoic acid (84 mg, 0.41 mmol), BOP reagent (148, 0.335 mmol), triethylamine (46,μL, 0;335 mmol) and dichloromethane (4 mL) were stirred at 20°C under Ar for 24 h. The reaction mixture was diluted with dichloromethane, washed with aqueous Na<sub>2</sub>CO<sub>3</sub>, water and brine, and dried over solid magnesium sulfate. The organic phase was filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica, 2% methanol/chloroform) to provide the title compound. The first the same of the Columnia Ligarity and the

d) (2R, 4S, 5S, 1'S) -5-(4-hydroxybutanoyl) amino-4-hydroxy-N-(1'o. 1305 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-386-3000 9.351 phenylmethylhexanamidey of to nounseque & of

25 A solution of the compound of Example 43(c) (177 mg) 0.236 mmol) and tetra-n-butylammonium fluoride: (2.84 mL, 2.84 mmol, 1M solution in THF) was stirred funder any argon by a matmosphere at room temperature overnights The solution was diluted with ethyl acetate, washed with saturated sodium 30 bicarbonate solution, and water, and the organic layer was concentrated. The residue was precipitated from the ethyl acetate solution to afford the title compound: NMR & (CD30D, 400 MHz) 7.0-7.3 (m, 10H), 6.86 (s, 2H), 4.62 (d, 1H), 4.05 (m, 1H), 3.43 (t, 2H), 2.55-2.90 (m; 4H) 7.2.60 (m, 1H), 2.17 (m, 2H), 2.05 (m, 1H), 1.76 (m, 1H), 1.67 (m, 2H), 1.55 (m, 1H), .88 (d, 3H), .72 (d, 3H); TLC Rf 0.40 (silica, 10%

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# Example 44

Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(benzyloxycarbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-

- 5 <u>imidazo-2-yllmethyl-hexanamide</u> as
- (a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-butyldimethylsiloxy-5-(benzyloxycarbonyl) valylamino-6-phenyl-N-(1'-isobutyl-1'-(imidazo-2-yl)) methyl-hexanamide.
- A solution of carbobenzyloxy-(L)-valine (50.4 mg, 0.20 and (110 mg, 0.20 mmol), the product of Example 13(a) (110 mg, 0.20 mmol), BOP state agent (88.7 mg, 0.20 mmol) and triethylamine (28 μl, 0.20 mmol) in methylene chloride (4 mL) was stirred at 25°C for 4 d. The reaction mixture was diluted with methylene chloride,
- washed with saturated sodium bicarbonate and the organic layer was concentrated. The product was purified by flash chromatography (silica gel, 4% CH2Cl2/ MeOH) to give the state a stitle compound (104 mg, 67%).
- (b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(benzyloxycarbonyl-valyl) amino-6-phenyl-N-(1'-isobutyl-1'imidazo-2-yl) methyl-hexanamide.

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To a solution of the compound of Example 44(a) (104 mg, 0.133 mmol) in MeOH (8 mL), 3N HCl (2 mL) was added. The

- 25.5 solution was stirred for 16 hrs at 25°C. The methanol was removed at reduced pressure and 10% sodium carbonate was 350 added to pH ~7.5. Ether (10 mL) was added and the solid
- in the product was: filtered and dried in vacuo to provide the title  $g_{\rm eff}$  [recompound (58 mg, 65%). NMR(CDCl3)  $\delta_{\rm c}$ 0.62%(d, 3H), 0.78 (d,
- ite 3011 3H), 0.82 (d, 3H), 0.90 (d, 3H), 1.62 (m, 2H), 1.96 (m, 1H),
  - $\texttt{seff} \quad \textbf{2.06} \quad (\texttt{m, v1H}) \,\,, \,\, \textbf{2.55} \,\,, \,\, (\texttt{m, 1H}) \,\,, \,\, \textbf{2.77} \,\,, \,\, (\texttt{m, 4H}) \,\,, \,\, \textbf{3.38} \,\,, \,\, (\texttt{s, 1H}) \,\,, \,\, \textbf{3.53}$
- Deta (m, 11H), 3.91 (M, 1H), 3.99 (m, 1H), 4.47 (d, 1H), 5.11 (s,
- ((ECV) 2H), 5.78 (d, (1H), 6.85 (s, 2H), 6.92-7.34 (m, 15H);

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## Example 45

Preparation of (2R,4S,5S,1'S)-2-phenylmethyl-4-hydroxy-5-(Nacetylvalyl) amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2yl)methyl-hexanamide

(a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-t-butyldimethylsil) oxy-5-(N-acetyl-valyl)amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2yl)methyl-hexanamide of a constitution of (128-2-mail) of a

To a solution of N-acetyl-(L)-valine: (40.3 mg, 0.253 mmol) in dry THF (8 mL) at -40°C was added n-methylmorpholine : (55.7 µl, 0.506 mmol) followed by isobutyl; chloroformate (33.5 µl, 0.253 mmol). The reaction mixture was stirred for 15 min, and the compound of Example 13(b) (139 mg, 0.253 mmol) in THF (3 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 d. reaction was diluted with ethyl acetate, and washed with water and brine. The organic solution was dried with sodium sulfate, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, 4% methanol/chloroform) to give the product as an oil (47 mg, 27%).

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(b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-25 acetylvalyl) amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2yl) methyl-hexanamide. in the englished his has an a

To a solution of the compound of Example: 45(a): (47 mg, 0.0681 mmol) in methanol (3 mL), 3N HCl (0.5 mL) was added. The reaction was stirred for 16 h at 25°C. The methanol was 30 removed under reduced pressure and the solution was diluted with water and neutralized with 5% sodium carbonate. The solid product was filtered, washed with water and ether, and dried in vacuo to yield the title compound (29.5 mg, (75%). NMR (CD3OD) δ 0.70 (d, 3H), 0:88 (m, 9H), 1.57 (m, 1H), 1.70 (m, 1H), 1.92 (s, 3H), 2.05 (m, 1H), 2.55 (q, 1H), 2.77 (m, 4H), 3.57 (d, 1H), 4.03 (m, 2H), 4.60 (d, 1H), 6.87 (s, 2H), 6.95-6.20 (m, 10H); MS m/e 575 [M+H]+.

# Portago of the late way of the contact to the Example 46.

Preparation of (2R,4S,5S,1'S)-5-[(imidazol-2-

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- y1) methyloxycarbonyllamino-4-hydroxy-N-(1'-isopropyl-1'-
- 5 5 imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
- in St.: a) (1-(benzyloxymethyl) imidazol-2-yl) methyl-(4-0)
- 20.0 (f nitrophenyl) carbonate (7) 10.0 Color of Color of Color
- Figure 13 Fig. amixture of bis(4-nitrophenyl)carbonate, (1-
  - 10 benzyloxymethyl)imidazol-2-yl)methanol and 4-

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- the procedure was reacted according to the procedure
  - -Enforcement Example 14(a) to afford the title compound (58%).
    - NMR (CDC13, 400 MHz)  $\delta$  8.18 (d, 2 H, J=8.38 Hz), 7.44-7.23 (m,
  - 380 (5, 7H), 7.11 (s, 1H), 7.13 (s, 1H), 5.48 (s, 2H), 5.44 (s, 2H),
  - 000.15 04.49 (8,92H) 108 to decide the month of the contract of the contract of the
- 3 b) (2R, 4S, 5S, 1'S) -5-((1-benzyloxymethyl) imidazol-2-
- actively methyloxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-
- o lisopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
  - 1 20 hexanamide: There is a dot that the Presente West and the way
- 3 A mixture of the compound of Example 46(a), (1)
- (ME (ME) (2R, 4S) 5S, 1'S) -5-amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
- 53 :: (322-y1) methyl-6-phenyl-2-phenylmethyl-hexanamide, and 4-
- dimethylaminopyridine was reacted according to the procedure
  - of Example 14(b) to afford the title compound (32%).
    - NMR (CDC13) 8 7.50-6.60 (m, 19H), 5.25 (m, 2H), 5.11 (d, 2H,
    - J=11.03 Hz), 4.68 (m, 1H), 4.39 (m, 2H), 3.97 (m, 1H), 3.67
    - (m, 1H), 2.88 (m, 1H), 2.72-2.28 (m, 6H), 1.85 (m, 1H), 1.60
- $3.00 \pm 0.00 \text{ (m, 1H)} = 0.92 \pm 0.817 \text{ (m, 15H)} = 0.807 \text{ (s, 3H)} = 0.067 \text{ (s, 3H)}$
- - c) (2R, 4S, 5S, 1'S)-5-(imidazoyl-2-yl-methyloxycarbonyl)amino-4-t-butyldimethylsiloxy-N-(1'-
- isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-1) 351- hexanamide: (Aynor's onal); (Aynor's onal)

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- The compound of Example 46(b) (58 mg, 0.073 mmol),
- profession methanol r(30mL), and 10% Pd on carbon (50 mg) were combined
- and stirred under 1 atm of H2 for 24 h. Additional catalyst

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(50 mg) was added and stirring under H<sub>2</sub> was continued for 8 h. The reaction was filtered through Celite®, concentrated and flash chromatographed (silica, step/gradient, 0-8% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to yield the title compound (28 mg/ 57%).

5 NMR(CDCl<sub>3</sub>) δ 7.29-6.83 (m, 14H); 5.05 (d; 1H, J=11.2 Hz), 4.91 (d, 1H, J=11.2 Hz), 4.71 (m, 1H), 3.92 (m, 1H), 3.61 (m, 1H), 3.02 (m, 1H), 2.81-2.54 (m, 4H), 2.36 (m, 1H), 1.93 (m, 1H), 1.59 (m, 1H), 0.91 (d, 3H, J=7.1 Hz); 0.89 (s, 9), 0.69 (d, 3H, J=7.1 Hz), 0.84-0.05 (m, 6H); MS(ES) m/e 673 [M+H]<sup>+</sup>.

d) (2R, 4S, 5S, 1'S) -5-(imidazol-2-yl-methyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide & state of rest 00 2 yellow 1863

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The compound of Example 46(c): (24 mg, 0.035 mmoL), 95% aqueous EtOH (0.50 mL), and concentrated aqueous HCl (0.050 mL) were stirred at 23°C for 24 h. The solution was diluted with H2O (5 mL) washed with EtOAc and then the aqueous phase was made basic by addition of solid K2CO3. (Extraction with EtOAc, concentration of the organic extract and trituration with CH2Cl2 afforded the title compound (14 mg, 72%). NMR (CDCl3) δ 7.33-6.85 (m, 14H), 5.11 (d, 1H, J=10.8 Hz), 4.96 (d, 1H, J=10.8 Hz), 4.47 (m, 1H), 3.72 (m, 1H), 3.38 (m, 1H), 2.81 (m, 4H), 2.59 (m, 1H), 2.07 (m, 1H), 1.72 (m, 1H), 1.62 (m, 1H), 0.78 (d, 3H, J=6.63 Hz), 0.67 (d, 3H, J=6.63 Hz); (m, 6H); MS(ES) m/e 559 [M+H]<sup>+</sup>.

## Example 47 . (211.70.81 3

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Preparation of (2R.4S.5S.1'S.1"RS)-5-((1"-(imidazol-2-yl)-2"methyl)propyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

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a) (1RS)-1-((1-benzyloxymethylimidazol-2-yl)-2-(3 a) methyl)propyl-(4-nitrophenyl)carbonate-1f-1ggg-gg-2

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A mixture of bis(4-nitrophenyl) carbonate, (1RS)-1-((1-benzyloxymethylimidazol-2-yl)-2-methyl) propanol and 4-dimethylaminopyridine was reacted according to the procedure of Example 14(a) to afford the title compound (61%). NMR

(CDCl<sub>3</sub>) & 8.18 (d, 2H, J=8.31 Hz), 7.38-7.21 (m, 7H), 7.13 (s, 1H), 6.94 (s, 1H), 5.74 (d, 1H, J=11.1 Hz), 5.47 (d, 1H, J=10.2 Hz), 4.53 (d, 1H, J=11.3 Hz), 4.41 (d, 1H, J=11.3 Hz), 2.64 (m, 1H), 1.18 (d, 3H, J=6.02 Hz), 0.87 (d, 3H, J=6.02 Hz); MS(ES) m/e 426 [M+H]<sup>+</sup>.

b): (2R, 4S, 5S, 1'S, 1"RS) -5-((1"-(1-benzyloxymethylimidazol-2y: yl)-2"-methyl-propyl)oxycarbonyl)amino-4-ts: butyldimethylsiloxy-N-(1'-isopropyl-1'-(1-(1"-(1-

10 benzyloxymethylimidazol-2-yl)-2"-

because methylpropyl)oxycarbonyl)imidazol-2-yl)methyl-6-phenyl-2becphenylmethyl-hexanamide?

of give of dale A mixture of the compound of Example 47(a) (145 mg, 0.33

mmol), the compound of Example 13(a) (75.9 mg, 0.14 mmol), 415 Tdimethylaminopyridine (41 mg, 0.33 mmol) and DMF (0.5 mL) was
15 stirred under argon for 18 h. The DMF was evaporated in
16 vacuo and the residue was combined with 10% aq K2CO3 (10 mL)
17 and extracted with EtOAc. The combined extracts were washed
18 with saturated aq NaHCO3, dried (K2CO3), filtered and

20 concentrated in vacuo. The residue was flash chromatographed = 1.001 (silica, step gradient, 0-4% MeOH/CH2Cl2) to afford the title = 2.1 compound (96.1 mg, 57%). NMR (CDCl3) & 7.38-6.78 (m, 26H), 5.67 (m, 1H), 15.61-5.00 (m, 6H), 4.58-4.27 (m, 5H), 3.97-3.61 (m, 3H), 2.78-2.10 (m, 8H), 1.95-1.51 (m, 2H), 1.10-0.55 (m, 27H), 10.50-0.05 (m, 6H).

imidazol-2-yl)-2"-methyl-propyl)oxycarbonyl]amino-4-hydroxy-

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for the back solution of the compound of Example 47(b): (81 mg, 0.07 mg, mmol), CH3OH (0.75 mL), and 3N aqueous HCl (0.25 mL) was stirred at 23°C for 20 h. The reaction mixture was diluted with H2O (10 mL), and washed with EtOAc (3 x 15mL). Solid 5 355 K2CO3, was added to give a basic solution (pH>12), which was extracted with EtOAc. The extracts were dried (K2CO3),

filtered, concentrated and flash chromatographed (silica, the step gradient, 0-8% CH3OH/CH2Cl2) to give the title compound

(34.9 mg, 65%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 7.43-6.79 (m, 9H), 5.87,

5.66 (2d, 1H, J=10.66, 10.85 Hz), 5.28 (m, 2H), 4.68 (m, 1H),

4.42 (m, 2H), 3.71 (m, 1H), 3.58 (m, 1H), 2.90-2.31 (m, 6H),

2.11 (m, 1H), 1.75, 1.51 (2m, 2H), 1.05, 0.97 (2d, 3H,

5 J=6.32, 6.45), 0.68 (m, 9H).

- d) (2R,4S,5S,1'S,1"RS)-5-((1"-(imidazol-2-yl)-2"-methyl)propyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenýlméthyl-hexanamide.
- A mixture of the compound of Example 47(c) (34 mg; 0.047 mmol), CH3OH (4 mL), and 10% Pd/C((34 mg), was stirred under H2 (1 atm) for 26 h. The suspension was filtered through Celite®, concentrated, and triturated with CH2Cl2 to yield the title compound (4 mg, 14%). <sup>1</sup>H NMR; (CDCl3/CD3OD) δ
  - 15 7.7.32-6.71 (m, 14H), 5.38 (m, 1H), 4.55 (m, 1H), 4.3.72 (m, 1H), 3.55 (m, 1H), 2.78 (m, 4H), 2.55 (m, 2H), 2.15 (m, 2H), 1.60 (m, 2H), 1.03-0.61 (m, 12H).

# Example 48 to the state of the state

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Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-isopropyl-1'-(4-(imidazoI-2-yl)imidazoI-2-yl)imidazoI-2-yl)lmethyl-6-phenyl-2-phenylmethyl-hexanamide

25 (a) (1'S)-1'-(carbobenzyloxy)amino-1'-isopropyl-1!-(4- as (imidazol-2-yl)imidazol-2-yl)methane

Cbz-(L)-valinal (0.45 g, 1.4 mmol) was stirred in anhydrous methanol at 0°C under argon. Glyoxal (40% in water) (0.22 mL, 1.4 mmol) and ammonium hydroxide (29% NH3) (0.88 mL, 14 mmol) were added and the mixture was allowed to stir at 0°C for 1 h. The cooling bath was removed and the solution stirred at room temperature for 16 h. The methanol was evaporated in vacuo and the residue was diluted with 5% aqueous HCl. After extracting with dichloromethane, the aqueous layer was made basic with solid sodium carbonate and extracted with dichloromethane. The combined organic extracts were dried over sodium carbonate, filtered, and evaporated to a solid which was chromatographed (silica, 4%

methanol/dichloromethane) to give the title compound (0.216 g, 43%) as a white solid. NMR (CDCl3)  $\delta$  7.15 (6H, s(br)), 6.88 (2H, s), 6.30 (1H, d), 4.89 (2H, dd), 4.52 (1H, t), 2.05 (1H, m), 0.73 (3H, d), 0.62 (3H, d). MS m/e 340.2 [M+H]<sup>+</sup>

(b) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N[1'-isopropyl-1'-(4-(imidazol-2-yl) imidazol-2-yl)] methyl-6phenyl-2-phenylmethyl-hexanamide

The compound of Example 48(a) (0.13 gm.) was dissolved
in anhydrous methanol with 10% Pd on activated carbon (0.02
g). Hydrogen gas was bubbled through the solution via
balloon for 1 h and the solution was stirred overnight under
a hydrogen atmosphere. The mixture was filtered through a
pad of Celite® and evaporated to yield 1'-amino-1'-isopropyl15 [4-(imidazol-2-yl)imidazol-2-yl]methane as a white solid
(0.13 g, 100%).

This compound was combined with the compound of Example 13(a) (0.334 g, 0.63 mmol), BOP reagent (0.28 g, 0.63 mmol), and triethylamine (0.13 mL, 0.945 mmol) in DMF (1 mL) and allowed to stir under Ar for 3 d. The DMF was evaporated in vacuo and the residue was diluted with dichloromethane. The solution was washed with water and brine. The organic layer was dried over sodium carbonate, filtered, and evaporated to yield (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-t-butyldimethysiloxy-N-[1'-isopropyl-1'-(4-(imidazol-2-yl) imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl hexanamide as

A portion of the solid (0.100 g, 0.14 mmol) was stirred in THF at room temperature under argon. Tetrabutylammonium fluoride; (0.84 mL, 0.84 mmol) was added and the mixture was allowed to stir for 16 h. The solution was diluted with water and extracted twice with dichloromethane. The combined organic extracts were washed with water and evaporated to an oily residue. The residue was dissolved in THF and several 35, drops of diethyl ether were added until a white precipitate formed. The precipitate was collected by filtration and dried in vacuo to yield the title compound as a white solid (76 mg, 90%). NMR (CD3OD) & 7.37-6.84 (13H, m), 4.61 (1H,

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d), 3.69 (2H, m), 3.54 (1H, d), 2.84-2.52 (5H, m), 2.06 (1H, m), 1.83 (2H, m), 1.57 (1H, m), 1.30 (9H, s), 0.87 (3H, d), 0.69 (3H, d); MS m/e 601.2 [M+H]+

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Example 49

Preparation of (2R:4S:5S.1'S)-5-[di(hydroxymethyl)methoxycarbonyllamino-4-hydroxy-N-(1'-isopropyl-1'-imidazol2-vl)methyl-6-phenyl-2-phenylmethyl-hexanamide

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a) di(t-butyldimethylsiloxymethyl) methyl-(4-nitrophenyl) carbonate

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A mixture containing bis (4-nitrophenyl) carbonate (1.89 g, 6.21 mmol), di(t-butyldimethylsiloxymethyl) methanol (2.00 g, 1 eq) and 4-dimethylaminopyridine (757 mg, 1 eq) in dichloromethane (100 mL) was stirred at room temperature for 2 d. The mixture was diluted with dichloromethane and washed with saturated aqueous Na<sub>2</sub>CO<sub>3</sub>, brine, and dried over Na<sub>2</sub>SO<sub>4</sub>.

The solvent was removed in vacuo, and the residue was

- 20 purified by flash chromatography (silica, 10% ethyi 6 compound (75%). NMR (CDCl<sub>3</sub>) δ 8.29 (2H, m), 7.37 (2H, m), 3,96 (1H, m), 3.85 (2H, d), 3.82 (2H, d), 0.89 (18H, s), 0.09 (12H, s).
- 25 b) (2R,4S,5S,1'S)-5-(di(t-butylear boutyldimethylsiloxymethyl) methyloxycarbonyl amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-16-phenyl-2-phenylmethyl-hexanamide and account to the second se

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A solution of di(t-butyldimethylsiloxymethyl) -methyl 4-30 nitrophenyl carbonate (475 mg, 0.974 mmol), the compound of Example 13(a) (178 mg, 0.325 mmol) and dimethylaminopyridine (119 mg, 0.974 mmol) in methylene choride was stirred at 20°C under Ar for 24 h. The solution was washed with aqueous Na<sub>2</sub>CO<sub>3</sub>, dried over solid Na<sub>2</sub>CO<sub>3</sub> and concentrated in vacuo.

35 Flash chromatography (silica; 4% methanol/dichloromethane) of the residue provided the intermediate (2R, 4\$, 5S, 1'S) -5- (di(t-butyldimethylsiloxymethyl) methyloxycarbonyl) amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-(1-(di(t-

butyldimethylsiloxymethyl) methyloxycarbonyl)imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide, which was dissolved in ether, washed with 10% NaOH, dried over Na<sub>2</sub>CO<sub>3</sub>, and concentrated to provide the title compound (197 mg, 71%).

5 NMR (CDCl<sub>3</sub>) & 7.43-7.05 (10H, m), 6.90 (2H, s), 6.65 (1H, bs), 5.09 (1H, d), 4.78 (1H, bd), 4.08 (1H, m), 3.89-3.50 (7H,m) 3.00-2.80 (4H, m), 2.65 (1H, m), 2.55-(2H, m), 1.90 (1H, m), 1.78 (1H, m), 1.10-0.85 (33H, m), 0.20-0.06 (18H, m), 2.55 (1H, m), 2.55 (1H,

c) (2R, 4S, 5S, 1'S) -5- (di (hydroxymethyl) methoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2phenylmethyl-hexanamide

A mixture containing the compound of Example 49(b) (50 mg) and ethereal HCl (4 eq) was allowed to stir in methanol:water (9:1) at room temperature overnight. The solvent was removed in vacuo, and the residue was diluted with ethyl acetate and washed with saturated aqueous Na<sub>2</sub>CO<sub>3</sub>. The product was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (29 mg, 94%). NMR (CD<sub>3</sub>OD) & 7.20-6.80 (10H, m), 6.71 (2H, s),-4.50 (1H, d), 3.90 (1H, m), 3.65-3.34 (5H, m), 2.82-2.45 (6H, m), 1.99 (1H, m), 1.74 (1H, m), 1.52 (1H, m), 0.78 (3H, d), 0.60 (3H, d).

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#### Example 50

Preparation of (2R.4S.5S.1'S)-5-(1-oxo-thian-4-yl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-30, yl)methyl-6-phenyl-2-phenylmethylhexanamide

Bridge Brook Reacting the compound of Example 32(b) (81 mg, .133mmol)

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Preparation of (2R.4S.5S.1 S)-5-((tetrahydrosulfonylpyran-4vl)oxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2v1) methyl-6-phenyl-2-phenylmethylhexanamide 303) 440 2

Reacting the compound of Example 50; (31 mg, 49.2 mol) with m-chloro perbenzoic acid (10 mg, 59.2 mmol), in methylene chloride yielded the title compound. NMR (CD30D) δ. 7.20-6.85 (10H, m), 6.76 (2H, s), 4.48 (1H, d), 3.68 (1H, m), 3.44(1H, m), 2.96-2.42 (9H, m), 2.32-2.04 (2H, m), 1.97-1.62 (4H, m), 1.61-1.43 (2H, m), 0.79(3H, d), 0.60 (3H, d); MS m/e 611.2 were to the long anguished the regularity of

# Example 52 the said to

Preparation of (2R.4S.5S.1'S)-5-(1.1-dimethyl-2-Idam acetoxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropylimidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

2012 (a) 0.(2R,4S,5S,1'S)-5-(1,1-dimethyl-2-) abolic limits in hydroxyethoxycarbonyl)amino-4-(t-butyldimethylsilyl)oxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2phenylmethyl-hexanamide

The compound of Example 38(b) (223 mg, 0.221 mmol) was dissolved in 10% aqueous methanol and combined with 1M HCl in ether (0.221 mL, 1 eq) at room temperature. After completion of the reaction the solvents were removed in vacuo. The residue was dissolved in dichloromethane and washed with aqueous saturated Na2CO3. The organic layer was concentrated and the residue was purified by flash chromatography (silica, 1 4% methanol/dichloromethane) to provide the title compound (138 mg, 94%). NMR (CDCl3) δ.7.38-6.81 (12H; m) / 4.93 + 4.65 (1H, d, rotamers), 4.81+ 4.48 (1H, t, rotamers), 4.15 + 4.08 (1H,d, rotamers), 3.90 (1H,q), 3.72 (2H, m), 3.50+3.38 (1H, 35 d, rotamers); 2.98-2.48 (5H, m); (2.35 (1H, m); 1.98 (1H; m); 1.79 (1H, m); 1.60 ((1H, m); 1.30 ((3h, s); 1.29 (3H,s), 1.09 -0.85 (15H, m), 0.79 (3H, d), 0.11 (6H, m).

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(11-isopropyl-1well :: Iimidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide

is the compound of Example 52(a) (103 mg, 0.155 mmol) was

W.H.5 stirred with acetic anhydride (30 mg, 0.309 mmol) and DMAP (40 mg, 0.309 mmol) in methylene chloride at room temperature , i.e. under argon overnight. The solvent was removed in vacuo and

the residue was flash chomatagraphed (silica, 4% 

The resulting 4-t-butyldimethylsiloxy intermediate (105 mg, 0.140 mmol) was stirred in methanol:water (9:1) with 1M HCl in ether (0.14 mL, 1 eq). The solvents were removed in - ight vacuo, the residue was diluted with dichloromethane, and the solution was washed with aqueous Na2CO3. The organic layer

1015 was concentrated and the residue was purified by flash's chromatography (silica, 5% methanol/dichloromethane) to  $_{\rm MD}$  or provide the title compound (82 mg, 91%). NMR (CD3OD)  $\delta$  7.29-

6.90 (10H, m), 6.81 (2H, s), 4.51 (1H, d), 4.05 (2H, s), 3.59(1H, m)/53.42 (1H, m), 2.80-2.45 (5H, m), 2.00 (1H, m),

(b) 2088; 1098 (3H, s), 1.72 (1H, m), 1.50 (1H, m), 1.34 (6H, d) 0.81

(m , H (3H, d), 00.60 (3H, d) . A S S S A A A

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### Example 53

- Preparation of (2R.4S.5S.1'S)-5-((1.1-dimethyl-2-(benzyloxycarbonylglycyloxylethoxycarbonyllamino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide hydrochloride salt
- 30 a) (2R, 4S, 5S, 1'S)-5-((1, 1-dimethyl-2carbobenzyloxyglycyloxy) ethoxycarbonyl) amino-4-(tbutyldimethylsilyloxy)-N-(1'-isopropyl-1'-imidazol-2-Www. (lyl) methyl-6-phenyl-2-phenylmethyl-hexanamide

The compound of Example 52(a) (100 mg, 0.151 mmol) was reacted with 2-chloro-1-methyl-pyridium iodide (92 mg, 0.36 369 (mmol), DMAP4(75 mg, 30.60 mmol) and Cbz-glycine (63 mg, 0.30 mmol) in methylene chloride (5 mL) under argon at reflux for 183 ht Solvents were removed in vacuo and the product was

purified by flash chromatagraphy (silica; 4%) (c)
methanol/dichloromethane) nto provide the title compound (95
mg, 73%). NMR (CDCl3) & 7.41-6.7111(17Hg/m) & 6.62g(1H, bs),
6.00 (1H,m), 5.20 (1H, m); 5.15 (2H; us); 64.832+ 4.55 (1H, d,
rotamers), 4.65+4.48 (1H; t; rotamers) & 4.81+4.38 (1H,q,
rotamers), 4.03 (1H,q); 4.02 (2H, d); 3:85+3.68 (2H, d,
rotamers), 2.85-2.48 (5H, m), 2.38 (1H, m); 1.905(1H, m),
1.55 (1H, m), 1.38 (3h, s); 1.29 (3H; s); 0:90 (9H; m), 0.85
(3H, d), 0.70 (3H, d), 0.11 (6H; m); rotameral off

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b) (2R, 4S, 5S, 1'S)-5-((1,1-dimethyl-2-(1,1-dimethyl-2-(1,1-dimethyl-2-(1,1-dimethyl-2-(1,1-dimethyl-2-(1,1-dimethyl-2-dimethyl-dispropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide hydrochloride salt (2013) (2013) (2013) (2013)

The compound of Example 53(a) (12 mg, 0.014 mmol) was stirred in methanol:water (9:1) with 1M HCl (2; eq) in ether overnight. The solvents were removed in vacuo to give the title compound (8 mg, 73%). NMR(CD3OD) δ 7.35 (2H,s), 7.31-6.85 (15H, m), 5.00 (2H, s), 4.59 (1H, d), 4.15 (1H, cd, rotamers), 4.65 + 4.48 (1H, t, rotamers), 4.81 + 4.38 (2H, dd), 3.80 (2H,d), 3.59 (1H, m), 3.40 (1H, d), 2.85-2.48 (5H, m), 2.00 (1H, m), 1.60 (1H, m), 1.55 (1H, m), 1.31 (3h, s), 1.29

(3H,s), 0.91 (3H, d), 0.60 (3H, d),

Example 54 Land Action and Action

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Preparation of (2R.4S.5S.1'S)-5-((1.1-dimethyl-2-ori.
glycyloxy)ethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide
dihydrochloride\_salt

a) (2R, 4S, 5S, 1'S) -5-(1, 1-dimethyl-2-1). (A dimethyl-2-1) (A dimethyl-2-1) (A dimethyl-2-1) (A dimethyl-2-1) (A dimethyl-3) (A dimethyl-3) (A dimethyl-1-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide (A dimethyl-3) (A dimethyl-3) (A dimethyl-3) (A dimethyl-3) (A dimethyl-3)

The compound of Example 53(a) (58 mg, ...0678mmol) was stirred in methanol with 10% Pd/C (50 mg), under 1 atm hydrogen overnight. The reaction mixture was filtered

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. (25) (14) (25), (27), (27), (35) (17), (27), (27)

through Celite® and the solvents were removed in vacuo to yield the title compound (48 mg, 98%). NMR(CD3OD) & 7.32-7.02 (10H, m), 6.99 (2H, s), 4.68 (1H, d), 4.40-4.28 (2H, dd), 3.81 (2H, d), 3.80-3.67 (2H, m), 2.90-2.49 (5H, m), 2.15 (1H, m), 5 1.97 (1H, m), 1.48 (1H, m), 1.40 (3H, s), 1.39 (3H,s), 1.15 (3H, d), 0.95 (9H, s), 0.70 (3H, d), 0.11 (6H, d).

b): (2R, 4S, 5S, 1'S)-5-((1, 1-dimethyl-2-glycyloxy) ethoxy-carbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide dihydrochloride salt

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The compound of Example 54(a) (43.5 mg, 0.060 mmol) was stirred in methanol:water (9:1) with 1M HCl in ether (0:12 mL, 2 eq) for 2 d. The solvents were removed in vacuo and the product was trituated with ether:methanol (20:1) to yield the title compound (40 mg, 98%). NMR(CD3OD) & 7.35 (2H, s), 7.30-6.92 (10H, m), 4.60 (1H, d), 4.25 (2H, dd), 3.75 (2H, d), 3.59 (1H, m), 3.49 (1H, m), 2.90-2.51 (6H, m), 2.10 (1H, m), 1.65 (1H, m), 1.54 (1H, m), 1.30 (6H, s), 0.90 (3H, d), 0.60 (3H, d).

#### Example 55

- 25 hydroxy)ethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-(4
  - isopropylcarbonylimidazol-2-yl))methyl-6-phenyl-2phenylmethyl-hexanamide dihydrochloride salt
  - a) (2R,4S,5S,1'S)-5-amino-4-t-butyldimethylsiloxy-N-[1'-
  - 30 isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
  - Using the procedure of Example 13(a), except substituting the compound of Example 28(d), the title compound was prepared.
- hydroxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-(4-

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isopropylcarbonylimidazol-2-yl))methyl-6-phenyl-2-:
phenylmethyl-hexanamide dihydrochloride salt

Following the procedures of Example 38(b) -38(c), except substituting the compound of Example 55(a) for (E);

5 (2R, 4S, 5S, 1'S) -5-amino-4-t-butyldimethylsiloxy-N-('- isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide, the title compound was prepared. NMR (CDCl3) & 7.49 (1H, s), 7.13 (5H, m), 6.84 (5H, m); 5.53 (1H, d), 4.47 (1H, d), 3.79 (1H, m), 3.60 (1H, m), 3.44 (2H, m), 3.16 (1H, m), 2.81-2.50 (5H, m), 1.92 (1H, m), 1.62 (2H, m), 1.18 (14H, m), 0.72 (3H, d), 0.58 (3H, d); MS m/e 621.4 [M+H]+.

# Example 56 Aprel 33 Careta

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Preparation of (2R.4S.5S.1'S)-5-((1S)-1-methyl-2hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide

Using the procedure of Example 41, except substituting 2(S)-t-butyldimethylsiloxy-1-methylethanol in 41(a) (prepared from 2(S)-1,2-propanediol), the title compound was prepared.

NMR(CD3OD) & 7.38-6.90 (10H, m), 6.83 (2H, s), 4.58 (2H, m), 3.61 (1H, m), 3.34 (3H, m), 2.82-2.44 (5H, m), 2.00 (1H, m), 1.66 (1H, m), 1.52 (1H, m), 1.08 (3H, d), 0.85 (3H, d), 0.60 (3H, d).

#### Example 57

Preparation of (2R.4S.5S.1'S)-5-((1R)-1-methyl-2- (hydroxyethoxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide

Using the procedure of Example 41, except substituting 2(R)-t-butyldimethylsiloxy-1-methylethanol in 41(a), the title compound was prepared. NMR(CD3OD)  $\delta$  7.39-6.88 (10H, m), 6.82 (2H, s), 4.56 (2H, m), 3.60 (1H, m), 3.36 (3H, m), 2.81-2.45 (5H, m), 1.99 (1H, m), 1.65 (1H, m), 1.51 (1H, m), 1.03 (3H, d), 0.84 (3H, d), 0.60 (3H, d).

# (to the deciding of Example 58

Preparation of (2R.4S.5S.1'S)-5-((1-acetyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

. The transfer of the beginning of the will be the control of the control of

5. phenylmethylhexanamide

The title compound was prepared by the procedure of Example 13(a)-(c), except substituting acetic anhydride in place of isopropyl chloroformate. NMR(CD3OD) δ 7.21-6.90 (10H, m), 6.81 (2H, s), 4.58 (1H, d), 3.98 (1H, m), 3.51 (1H, m), 2.85-2.49 (5H, m), 1.99 (1H, m), 1.68 (3H, s), 1.61 (3H,

. (t) m), 1.50 (1H, m), 0.80 (3H, d), 0.60 (3H, d).

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- hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4-benzyloxyphenylmethyl) hexanamide
  - a) (3R,5S,1'S)-(1'-t-butoxycarbonylamino-2'-phenyl)ethyl-3-± 20.5 (4-benzyloxy)phenylmethyl-tetrahydrofuran-2-one 200 62
- (4-benzyloxy) benzyl bromide, the title compound was prepared (284 mg, 27%). NMR(CDCl3) & 7.48-6.72 (14H, m), 4.94 (2H,
  - pn s s), 4.43((1H, d); 44.12 (1H, dd); 3.83 (1H, q); 2.97-2.62 (5H, 2H, m); 2.12m(1H, m); 1.85(1H, m); 1.27 (9H, ms);
  - (p.,15b) (2R,4S,5S)=5-(t-butoxycarbonyl) amino-4-t-butyldimethyl-, it is siloxy-6-phenyl-2-(4-benzyloxyphenylmethyl) hexanoic acid

    Folowing the procedure of Evans et al., J. Org. Chem.

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30 50, 4615 (1985), except substituting the compound of Example 59(a) for benzyl bromide, the title compound was prepared.

NMR(CDCl3) δ 7.42-6.76 (14H, m), 4.99 (2H, s), 4.69 (1H, d),

3.91 (1H, q), 3.66 (1H, m), 2.98-2.36 (5H, m), 1.85 (1H, m),

1.52 (1H, m), 1.30 (9H, s), 0.88 (9H, s), 0.04 (6H, m).

recording the control of the control

c) (2R,4S;5S,1'S)-5-(t-butoxycarbonyl)amino-4-tbutyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl6-phenyl-2-(4-benzyloxyphenylmethyl) hexanamide

Following the procedure of Example 12(c), except using (b), the title compound was prepared (284 mg, 92%).

NMR(CDCl3) δ 7.42-6.74 (16H, m), 5.041(2H, s), 4.99 (1H, d),

4.77 (1H, d), 4.51 (1H, dd), 3.93 (1H, g), 13.69 (1H, m),

5 2.80-2.39 (5H, m), 1.81 (1H, m), 1.62 (1H, m), 1.33 (9H, s),

0.92 (9H, s), 0.75 (6H, dd), 0.07 (6H, d);

(2R 48.55.1'S)-5-(t-butoxycarbonyl)amino-4-bydroxy-N-(1'-

isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(4-0.)

10 benzyloxyphenylmethyl) hexanamide (11) 24.5-28.5 (14 0.1

Following the procedure of 12(d), except using (c), the title compound was prepared (100 mg, 94%). NMR(CD3OD) δ 7.41-7.09 (10H, m), 6.85 (2H, d), 6.79 (2H, s), 6.58 (2H, d), 5.41 (1H, d), 4.90 (2H, s), 4.47 (1H, d), 3.62 (1H, q), 3.48 (1H, d), 2.79-2.48 (6H, m), 2.02 (1H, m), 1.62 (2H, m), 1.33 (9H, s), 0.74 (3H, d), 0.61 (3H, d).

#### Example 60

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- Following the procedure of Example (4 (b), except using the compound of 59 (d), the title compound was prepared (56 mg, 86%). NMR (CD3OD) δ 7.18 (5H, m), 6.84 (2H, s), 6.73 (2H, d), 6.44 (2H, d), 5.32 (1H, d), 4.45 (1H; d); (3.61 ((1H, q), 3.42 (1H, m), 2.80-2.42 (5H, m), 2.04 (1H; m), 1.61 (2H, m), 1.31 (9H, s), 0.70 (3H, d), 0.61 (3H; d) 21 (0.63)

ales de la figure (1981) d'Ul (1986). Sera d'**Example 61** (1986) de la company de la c

trace and said (2) the (graders

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Preparation: of (2R:4S:5S)-5-(t-butoxycarbonyl)amino-4hydroxy-2-phenylmethyl-6-phenyl-N-[1:-cyclopropyl-1:-

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35 imidazol-2-vllmethvl-hexanamide

a)  $\alpha$ -(t-butoxycarbonyl)-amino- $\alpha$ -cyclopropylacetonitrile

Operation of the property of the contract of the

To a solution of cyclopropylmethanol (10.2 g, 141 mmol)

iver a in methylene chloride (250 mL) sodium acetate (1 g) and 20 g

of Celite® were added. Pyridinium chlorochromate (30 g, 140

on mmol) was added in small portions over a period of 30 m.

So After 1 h the reaction mixture was diluted with ether

(100mL), filtered through Celite® and washed with ether. The combined organic extracts (1 L) were concentrated in vacuo at 15-18°C to yield formyl cyclopropane.

The crude aldehyde was dissolved in water (50 mL), and ammonium chloride (6.51 g), potassium cyanide (7.16 g) and aqueous ammonium hydroxide (100 mL, 28% w/w). The reaction mixture was stirred at room temperature overnight, extracted with ethyl acetate, and the combined organic extracts were dried over MgSO4. Filtration and evaporation of the solvent in vacuo yielded α-amino-α-cyclopropyl acetonitrile as an oil.

To a solution of the crude aminonitrile (2 g) in THF (20 mL) di-tert-butyldicarbonate (1.53 g, 7 mmol) was added. The reaction was stirred overnight. Removal of the solvent in 20 vacuo followed by flash chromatography (silica, 1:8 ethyl acetate:hexane) yielded the title compound (2.8 g). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 200 MHz) δ 5.0 (bs, 1H), 4.4 (bs, 1H), 1.4 (s, 9H), 1.2 (m, 1H), 0.7 (m, 2H), 0.5 (m, 2H).

To a solution of the compound of Example 61(a) (1 g, 5.1 mmol) in THF (20 mL), diisobutylaluminium hydride (10.5 mL, 10.5 mmol). 1M in THF) was added at -78°C, over 5 min. The reaction mixture was allowed to warm to 0°C over a period of 2 h, and stirred at 0°C for an additional 1 h. The reaction mixture was quenched with MeOH (2 mL), and saturated potassium sodium tartrate solution (100 mL) was added.

Extraction with ether, drying over MgSO4 and removal of solvents in vacuo yielded an oil.: Flash chromatography 35 (silica, 1:10 ethyl acetate:hexane) gave the title compound as a colorless solid (225 mg). NMR(CDCl3, 400 MHz) & 9.45 (bs, 1H), 4.95 (bs, 1H), 3.5 (bs, 1H), 1.3 (s, 9H), 0.7 (m, 1H), 0.3-0.6 (m, 4H).

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c) 1-(t-butoxycarbonyl)amino-1-(imidazol-2-ŷl)-1-cyclopropyl-methane

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A mixture of the compound of Example 61(b) (178 mg, 0.89 mmol), glyoxal (150 mL, 1 mmol, 40% aq), ammonium hydroxide (5 mL, 28% aq) and MeOH (5mL) was stirred at room temperature for 10 h. The solvents were removed in vacuo and the residue was titurated with ether to yield a brown solid (53 mg). The solid was passed through Florisil® and eluted with 5% MeOH/methylene chloride. Removal of the solvent in vacuo followed by trituration provided the title compound as a colorless solid (19 mg). MS(CI/NH3) m/e 238.3 [M+H]+. 1H NMR(CD3OD, 200 MH2) & 6.9 (s, 2H), 4.1 (bd, 1H), 1.4 (s, 9H), 1.3 (m, 1H), 0.6 (m, 2H), 0.4 (m, 2H).

d) 1-amino-1-(imidazol-2-yl)-1-cyclopropyl-methene, trifluoroacetate

mL of TFA and stirred at room temperature for 20 min.

Solvents removed in vacuo to give the title compound as a

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semisolid residue. <sup>1</sup>H NMR(CD<sub>3</sub>OD, 200 MHz) 87.1 (s, 2H), 3.8 (d, 1H, J=7 Hz), 1.5 (m, 1H), 0.5-0.8 (m, 4H).

e) (2R,4S,5S)-5-(t-butoxycarbonyl)amino-4-(t-butyldimethyl)25 siloxy-2-phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol2-yl]methyl-hexanamide

The compound of Example 61(d) was dissolved in DMF (2 mL) and NMM (26 mg, 0.25 mmol) was added and the solution was stirred at 0°C for 30 min. (2R,4S,5S)-2-phenylmethyl-4-(t-butyldimethyl)siloxy-5-(t-butoxycarbonyl)amino-6-phenyl hexanoic acid (38 mg, 0.07 mmol) and BOP reagent (30 mg, 0.07 mmol) were added and the reaction was stirred at room temperature for 24 h. The reaction was diluted with ethyl acetate (100 mL), washed with aqueous sodium bicarbonate and dried over anhydrous potassium carbonate! Removal of solvents in vacuo, followed by flash chromatography (silica, 5% methanol/methylene chloride) yielded the title compound as a mixture of diastereomers (25 mg) is a silvent of the solvent of diastereomers (25 mg) is a silvent of diastereomer of diastereomers (25 mg) is a silvent of diastereomer of diaster

phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-yl]methyl-hexanamide

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The compound of Example 61(c) was dissolved in THF (2 mL) and tetrabutyl ammonium fluoride (200mL, 1M in THF) was added. The reaction was stirred at room temperature overnight and methylene chloride (100 mL) and water (10 mL) were added. The organic layer was dried over potassium

10 carbonate, and the solvent was removed in vacuo to give an oil. Flash chromatography (silica, 5% methanol/methylene chloride) gave a colorless solid which was a 1:1 diastereomeric mixture of the title compound.

Example 62

Preparation of (2R.4S.5S.1'R)-5-(t-butoxycarbonyl) amino-4hydroxy-2-phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'imidazol-2-yllmethyl-hexanamide: and

20 (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-2phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2yllmethyl-hexanamide

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25 61(e) by flash chromatography (silica, 3% methylene chloride/methanol), yielded 48 mg of isomer 1, 15 mg of isomer 2 and 20 mg of combined fractions. H NMR for isomer 1 (CDCl<sub>3</sub>, 400 MHz) 87.1-7.4 (m, 10H), 6.95 (s, 2H), 6.1 (d, 26 to 5 1H), 4.85 (d, 1H), 4.15 (dd, 1H), 3.75(q, 1H), 3.6(m, 1H), 30 2.9 (dd, 1H), 2.7 (d, 2H), 2.6 (dd, 1H), 2.3 (m, 1H), 2.0 (m, 2 to 1H), 1.6 (m, 1H), 1.4 (m, 1H), 1.35 (s, 9H), 0.95 (s, 9H), 0.7 (m, 3H), 0.4 (m, 1H), 0.25 (m, 1H), 0.1 (m, 1H), 0.2 (s, 3H), 0.1 (s, 3H), 1.4 (m, 1H), 6.26 (d, 1H), 4.6 (d, 1H), 4.0 (m, 35 2H), 2.5-3.0 (m, 4H), 1.8 (m, 1H), 1.7 (m, 1H), 1.5 (m, 1H), 1.4 (s, 9H), 1.0 (s, 9H), 0.7 (m, 2H), 0.2 (m, 2H), 0.1 (2 overlapping singlets, 6H).

b) Following the procedure of Example 61(f), except substituting the compounds of Example 62(a) yielded the title compounds. 1H NMR for isomer 1 (CD3OD, 400 MHz) 87.1-7.3 (m, 10H), 6.95 (s, 2H), 4.25 (d, 1H), 3.5-3.7 (m, 2H), 2.5-3.0 (m, 5H), 1.7 (m, 2H), 1.4 (s, 9H), 1.1 (m, 1H), 0.6 (m, 1H), 0.25-0.4 (m, 2H), 0.05 (m, 1H); MS (ESMS) m/e 533.2 [M+H]+; 1H NMR for isomer 2 (CD3OD) 87.1-7.4 (m, 10H), 6.85 (s, 2H), 4.25 (d, 1H), 3.5-3.7 (m, 2H), 2.5-2.9 (m, 5H), 1.5-1.8 (m, 2H), 1.4 (s, 9H), 1.1 (m, 1H), 0.2-0.6 (m, 4H); MS (ESMS) m/e 533.4 [M+H]+.

### Example 63 warp to another to

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Preparation of (2R,4S,5S,1'S)-5-((isopropylthiol)carbonyl)
amino-4-hydroxy-2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'imidazol-2-yllmethyl-hexanamide

butyldimethylsiloxy-2-phenylmethyl-6-phenyl-N-[1'-isopropyl1'-imidazol-2-yl]methyl-hexanamide (81 mg, 148 mmol) and DMAP

(37 mg, 303 mmol) in dichloromethane (8 mL), (3 mol) in dichloromethane (1 mL) was added. The solution was stirred for 20 h and an additional equivalent of the chloroformate and DMAP were added. The reaction mixture was stirred for an additional 20 h, diluted with dichloromethane, and washed with saturated sodium bicarbonate. The organic extract was dried over magnesium sulfate, filtered and evaporated to an oil. The oil was dissolved in chloroform and purified by flash chromatography (silica, 1% methanol/chloroform) to give the title compound as an oil (79.5 mg).

hydroxy-2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'-imidazol-2-yl]methyl-hexanamide

yl]methyl-hexanamide

To a solution of the compound of Example 63(a) (79 mg,

105 mmol) in methanol (8 mL), 10% hydrochloric acid (3 mL)

was added. The reaction mixture was stirred overnight at

25°C. The methanol was evaporated in vacuo, and the residue

was diluted with water. The solution was neutralized with 5%

aqueous sodium, carbonate, and a solid precipitated. The

solid was filtered, washed with water, and triturated with

compound (27 mg, 48%). NMR(CDCl3, 250 MHz) & 6.9-7.3 (m,

10H), 6.85 (s, 2H), 6.20 (d, 1H), 4.42 (d, 1H), 4.22 (m, 1H),

4.0 (m, 1H), 3.55 (m, 3H), 2.5-3.0 (m, 6H), 1.65 (t, 2H),

115: 1.27 (m, 7H), 7.71 (d of d, 6H); MS(FAB) m/e 537 [M+H]<sup>+</sup>; TLC

Rf 0.30 (silica, 4% methanol/chloroform).

#### Example 64

Preparation of (2R.4S.5S.1'S)5-(1-hydroxymethyl-(Ar 11: //cyclopentyloxycarbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexamide

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a) 1-(t-butyldimethysiloxy) methyl-cyclopentanol
25 plTo a solution of 1-hydroxymethyl-1-cyclopentanol (4.07
g, 0.035 mole) in dichloromethane (30 mL) t-butyldimethylsilyl chloride (5.28 g, 0.035 mol) in dichloromethane (30 mL)
was added. Triethylamine (5.37 mL, 0.0385 mol) and DMAP
(0.171 g, 0.0014 mol) were added and the solution was stirred
30 overnight at 25°C. The solution was diluted with
dichloromethane (30 mL) and washed with water and saturated
31 ammonium chloride solution. The organic solution was dried
32 over sodium sulfate, filtered and the solvent removed at
33 chromatography (silica, 19:1 hexane:ethyl acetate) to yield
the title compound as a colorless oil (6.95 g, 86%).

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b) 1-(t-butyldimethylsiloxy) methyl-cyclopentyl 4-nitrophenyl carbonate

A solution of the compound of 64(a) (1.15 g, 5 mmol),

DMAP (0.611 g, 5 mmol) and bis (4-nitrophenyl) carbonate (1.52
g, 5 mmol) in dichloromethane (16 mL) was stirred overnight

at 25°C. The reaction mixture was diluted with

dichloromethane and washed with 5\* sodium carbonate. The

solvent was removed at reduced pressure and the residual oil

was triturated with hexane:ethyl acetate (3:2) and filtered.

The product was purified by flash chromatography (silica,

19:1 hexane:ethyl acetate) to give a colorless oil (0.599 g,

30%).

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c) (2R,4S,5S,1'5)-5-[1-(t-butyldimethylsiloxy)methyl
cyclopentyloxycarbonyl]amino-4-t-butyldimethylsiloxy-N-[1'isopropyl-1'-(t-butyldimethylsiloxy)methyl
cyclopentyloxy)imidazol-2-yl]-6-phenyl-2-phenylmethylhexanamide

A solution of the compound of Example 13(a) (173 mg, 0.316 mmol), DMAP (81 mg, 0.663 mmol) and the compound of Example 64(b) (262 mg, 0.663 mmol) in dichloromethane (10 mL) was stirred for 48 h at 25°C. The organic solution was diluted with dichloromethane, washed with 5% sodium carbonate solution and the solvent removed at reduced pressure. The product was purified by flash chromatography (silica, 4:1hexane:ethyl acetate) to yield the title compound as an oil (200 mg, 60%).

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d) (2R, 4S, 5S, 1'S) 5-(1-hydroxymethyl-cyclopentyloxy-carbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexamide so so the i

A solution of the silated derivative (200 mg, 0.188 mmol) in methanol (7 mL) and 3N HCl (2.5 mL) was stirred overnight at 25°C. The methanol was removed at reduced pressure and the solution was diluted with water (15 mL) and extracted with ether (25 mL). The aqueous solution was neutralized with 5% sodium carbonate solution to pH 7-7.5 and the product precipitated as a solid. The solid was filtered,

washed with water and dried in vacuo to yield the title compound (51 mg, 47%). NMR (CD3OD, 400 MHz) δ 7.0-7.3 (m, 10H), 6.87 (s, 2H), 4.62 (d, 1H), 3.70 (m, 3H), 3.55 (d, 1H), 2.5-2.9 (m, 5H), 2.05 (m, 1H), 1.5-2.0 (br, 10H); 0.88 (d, 3H), 0.70 (d, 3H); TLC R<sub>f</sub> 0.50 (silica, 8% methanol/chloroform).

## Margan, and the species of the latter of Example 65

- Preparation of (2R.4S.5S.1'S)-5-[3-(R)-(1H-imidazol-2-yl)-3
  hydroxy-4-methylpentylamidol-4-hydroxy-N-(1'-isopropyl-1'
  imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide; and

  (2R.4S.5S.1'S)-5-[3-(S)-(1H-imidazol-2-yl)-3-hydroxy-4
  methylpentylamidol-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
- 15. yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

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- ( a) 1-(1-benzyloxymethylimidazol-2-yl)-2-methyl-1-propanol 1 30% 70% - 1-benzyloxymethylimidazole prepared according to the procedure of Ngochindo, R., J. Chem. Res. (S), 58 (1990)) , dropwise with n-BuLi (8.4 mL, 21 mmol, 2.5M in hexane). The get resulting solution was stirred at:-40°C for 15 min, and i-Morarge butyraldehyde (2.0 mL, 22 mmol) was added dropwise. The at a reaction was stirred at -40°C for 1.5 h, 0°C for 1 h, warmed 25 to 23°C, poured into H2O, and extracted with EtOAc. The combined extracts were washed with brine, dried (Na2SO4) and and a concentrated in vacuo. Trituration of the residue with Et20/hexane gave a white solid which was dried in vacuo overnight to afford of the title compound (3.57 g, 69%). 30 NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  7.28 (m, 5H), 6.97 (s, 1H), 6.92 (s,  $(d_r - 1H)_r = 5.23 \cdot (d_r - 1H)_r = 12 \cdot Hz)_r = 5.42 \cdot (d_r - 1H)_r = 12 \cdot Hz)_r = 4.48 \cdot (s_r - 1H)_r = 12 \cdot Hz)_r = 12 \cdot Hz_r = 12 \cdot$ 2H), 4.44 (d, 1H, J=9 Hz), 2.21: (m, 1H), 1.02 (d, 3H, J=77 172 Hz), 10.83 (d, 3H, J=7 Hz) 10.000 ( ) 10.000 ( )
- (35: b): 1-(benzyloxymethylimidazol-2-yl)-2-methyl-propan-1-one
  (19: 10. The compound of Example 65(a) (1.0 g; 3.88 mmol), MnO2,
  (1.69 g, 19.4 mmol), and CH2Cl2 (75 mL) were combined and
  (1.1) Exircle for 1 d. Additional MnO2 (1.69 g, 19.4 mmol) was

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added and stirring was continued for an additional 2 d. Filtration through Celite®, concentration and flash chromatography (silica, 0-1% CH3OH/CH2Cl2) afforded the title compound (0.773 g, 77%). 1H NMR (CDC13, 400 MHz)-7.28 (m, 6H), 7.18 (s, 1H), 5.85 (s, 2H), 4.52 (s, 2H), 3.94 (m, 1H), methanol/chloseform). 1.21 (d, 2H, J=5 Hz).

c) t-butyl 3-(1-benzyloxymethylimidazol-2-yl)-3-hydroxy-4methyl-pentanoate

Diisopropylamine (83 µL, 0.59 mmol) and THF1 (1.5 mL) were cooled to -40°C and n-BuLik (188 µL to 0.47% mmol, 2.5M in hexane) was added. The reaction mixture was warmed to -10°C and stirred for 15 m, recooled to -70°C and t-butyl acetate (63 μL, 0.47 mmol) was added. The reaction was stirred for 5 m, and HMPA (254 µL, 1.41 mmol) was added The reaction was stirred at -70°C for 5 m and 1-(benzyloxymethylimidazol-2yl)-2-methyl-propan-1-one (100 mg; 0:39 mmol) in THF (1.5 mL) was added dropwise. The mixture was stirred at -70°C for 30 m, -40°C for 30 m, -10°C for 30 m, swarmed to 23°C, poured 20 into 10% aqueous K2CO3 and extracted with EtOAc. The combined organic extracts were washed with brine, dried (K2CO3), concentrated and flash chromatographed (silica gel, step gradient, 0-20% EtOAc/hexanes) to afford the title compound increase (131 mg, 90%). 1H NMR(CDCl3, 400 MHz) δ 7.25 (m, 55H), 6.96 25 (s, 1H), 6.91 (s, 1H), 5.69 (d, 1H, J-10 Hz), 5.65 (d, 1H, J=10 Hz), 4.53 (d, lH, J=11 Hz), 4.48 (d, lH, J=11 Hz), 3.23 (d, 1H, J=6 Hz), 2.57 (d, 1H, J=6 Hz), 2.14 (m, 1H), 1.39 (s, 9H); 0'.97 (d, 3H, J=7 Hz); 0.75 (d, 3H, 5 J=7 Hz); MS(ES) m/e that his to bear a relationary 375 [M+H]+. MERICO 2200 100 Mars 6 21 3 mg - 10

> d) 3-(1-benzyloxymethylimidazol-2-yl)-3-hydroxy-4-methyl

The compound of Example: 65(c) (93 mg. 0.24 mmol) was dissolved in TFA (1 mL) and stirred for 20 m. The TFA was removed in vacuo to give the title compound (102 mg;d 100%). 1H NMR (CDC13, 400 MHz) 7.30 (m, 7H); 6.06 (d, 1) H, J=9 Hz), 5.74 (d, 1H, J=1 Hz), 4.67 (d, 1H, J=9 Hz), 4.61 (d, 1H, J=9 Hz), 3.62 (d, 1H, J=12 Hz), 2.93 (d, 1H, J=12 Hz), 2.04 (m,

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3 (d, 3H, J=12 Hz); MS(ES) m/e 6 main [ M+H] + by; MS(ES) m/e
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- N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2
  - phenylmethyl-hexanamide
- -: A mikture of the compound of Example 65(d) (1.0 eq)
  (2R,4S,5S,1'S)-5-amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
- 38.810 2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (1.1 eq), BOP (1.1 eq), and triethylamine (4 eq) were reacted
  - (iii . . .) according to the procedure of Example 1(c). The product was
- purified by flash chromatography to afford the title compound (57%) (silica, step gradient, 0-4% CH3OH/CH2Cl2). <sup>1</sup>H
  - 15 NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.36-6.76 (m, 19H), 5.65 (m, 2H), 4.66
  - (m, 1/2H), 4.51, (m, 2H), 4.39 (m, 1/2H), 4.30 (m, 1/2H), 4.02 (m, 1/2H), 3.68 (m, 1H), 3.28 (m, 1H), 2.90-2.35 (m, 6H),
- 2.13 (m, 1H), 1.76 (m, 1/2H), 1.68 (m, 1/2H), 1.40 (m, 1/2H),
- 1.00-0.70 (m, 21H), 0.10-0.00 (m, 6H); MS(ES) m/e 849 [M+H]+.
- A (Hill 20, a) That I was the property of the first and the second of the second of the first of
- (35.1 ...) f) ...(2R, 4S, 5S, 1.!S) =5-[3-(RS)-(1-benzyloxymethylimidazol-2-yl)-3-hydroxy-4-methylpentanoyl]amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

  The compound of Example 65(e) (100 mg, 0.12 mmol) was
- desilylated by the procedure of 47(c) to cleanly afford the title compound (78 mg, 89%). 1H NMR(CDCl3, 400 MHz) & 7.40
  - med. me6.80 (m, 19H), 5.75 (m, 2H), 4.97 (m, 1/2H), 4.78 (m, 1/2H),
  - 4.51 (m, 2H) 3.94 (m, 1/2H), 3.85 (m, 1/2H), 3.51 (m, 1H),
    - 3.21 (m, 1H), 2.97-2.43 (m, 6H); 2.00 (m, 1H), 1.60 (m, 1H),
  - 30 -1.43 (m, 1H), 0.97-0.49 (m, 12H); MS(ES) m/e 735 [M+H]+:
- -fyddew(:g) (2R,4S,5S;1'S)-5-[3(R),-(imidazol-2-yl)-3-hydroxy-4-methylpentanoyl]amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-
- paints: 2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide; and

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- -:-135 ala (2R, 4S, 5S, 1'S) -5-[3-(S)-(imidazol-2-yl)-3-hydroxy-4-
- 17 life methylpentanoyl]amino-4-hydroxy-N-(1\*-isopropyl-1\*-imidazol-

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Using the procedure of Example 47(d), the compound of Example 65(f) (72 mg, 0.98 mmol) was hydrogenated to afford a diastereomeric mixture of the title compounds. The mixture was purified by flash chromatography (silica, step gradient, 0-8% CH3OH/CH2Cl2) to afford tail fractions containing the pure diastereomers (35 mg total, 58%).

Isomer 1, last eluting, (2R, 4S, 5S, 1'S)-5-[3-(R)-(1H-Imidazol-2-yl)-3-hydroxy-4-methylpentylamido]-4-hydroxy-N
(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2
phenylmethyl-hexanamide. <sup>1</sup>H NMR(CDCl<sub>3</sub>, 400! MHz) & 7.35-6.82

(m, 10H), 6.93 (s, 1H), 6.84 (s, 1H), 4.42 (d, 1H, J=9 Hz),

3.77 (m, 1H), 3.40 (m, 1H), 3.00-2.40 (m, 5H), 2.14 (m, 1H),

1.99 (m, 1H), 1.56 (m, 1H), 1.47 (m, 1H), 0.93-0.64 (m, 12H);

MS(ES) m/e 615 [M+H]+.

Isomer 2, first eluting, (2R, 4S, 5S, 1'S) -5-[3(S)-(1H-Imidazol-2-yl)-3-hydroxy-4-methylpentylamido]-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-, phenylmethyl-hexanamide. <sup>1</sup>H NMR(CDCl<sub>3</sub>, 400 MHz) & 7.35-6.81 (m, 10H), 6.83 (s, 1H), 6.81 (s, 1H), 4.46 (d, 1 H, J=9 Hz), 3.93 (m, 1H), 3.40 (m, 1H), 3.00-2.40 (m, 5H), 2.13 (m, 1H), 1.91 (m, 1H), 1.41 (m, 1H), 1.10 (m, 1H), 0.93-0.64 (m, 12H); MS(ES) m/e 615 [M+H]<sup>+</sup>.

#### Example 66

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Preparation of (2R.4S.5S.1'S)-5-[(4-methoxyphenoxy)carbonyll-amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide

a) (2R, 4S, 5S, 1'S) -5-[(4-methoxyphenoxy) carbonyl]amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(N'-'methoxycarbonyl)imidazol-2-yl]methyl-6-phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example (13(b); except using p-methoxyphenyl chloroformate and (2R, 4S, 5S, 1'S) -5-amino-4-t-butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide (114 mg, 0.21 mmol), the title compound was prepared (63%). NMR (CDCl<sub>3</sub>), 8 7.44-6.76

(s,3H), 3.76 (m, 1H), 3.73 (s, 3H), 2.96-2.50 (m, 5H), 2.05 (m, 5H), 1.60 (m, 1H), 0.94 (s, 9H), 0.79 (d, 3 H, J=7 Hz), THE (1980.74 (S, 73H)) 0.12 (S, 3H) -10.11 (S, 3H) 1. 11

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√ = + b) (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide with the bear in th there is no see that a

Following the procedure of Example 13(c), except using so 10 or the compound of Example 66(a), the title compound was at prepared (32%). NMR(CDCl3/CD3OD), δ 7.36-6.84 (m, 16H), 4.49 (d, 1H, J=9 Hz), 3.79 (s, 3H), 3.37 (m, 1H), 2.92-2.60 (m, 5H), 2.10-1.70 (m, 3H), 0.78 (d, 3H, J=7 Hz), 0.67 (d, 3H, (x = J=7 Hz); MS(ES) m/e 585 [M+H]+.

V: 15 (5) (3) (3) (4) (5) (7) (4)

etalia) de son 6200 Example 67

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Preparation of (2R.4S.5S.1'S)-5-(t-butylaminocarbonyl)amino -4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-

20 phenylmethyl-hexanamide

a) (2R, 4S, 5S, 1'S) 5-(t-butylaminocarbonyl) amino-4-(tbutyldimethylsiloxy)-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide 1997 to kyssion gra. ordat.

11 25 25 The compound of Example 13(a) (0.13 g, 0.24 mmol) was id to dissolved in dichloromethane (3 mL) and t-butyl isocyanate (0.028 g, 0.29 mmol) was added. After stirring at 30°C for was removed under reduced pressure and the id. residue was chromatographed (silica, 2:3 ethylacetate:hexane) .30 . to give the title compound as a white solid (0.12 g, 77%). NMR (CDCl3), (δ.7.35-7.05) (12H, m), 6.85 (2H, s), 4.69 (1H, d,

J=9 Hz), 4.60 (1H, t, J=8 Hz), 4.38 (1H, br), 4.24 (1H, q, J=8 Hz), 3.66 (1H, dd, J=4 Hz, 10 Hz), 2.95 (1H, dd, J=9Hz, 13Hz), 2.73(2H, m), 2.54 (1H, dd, J=5 Hz, 13 Hz), 2.42 (1H, m), 1.82 (1H, m), 1.67 (1H, m), 1.22 (9H, s), 0.93 (9H, s), 2 12 12 13 0.84 (3H, d, (J=7.Hz), 0.79 (3H, d, J=7 Hz), 0.08 (3H, s),

0.071 (3H, 4s); MS (ES) m/e 648.4 [M+H]+.

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(2R, 4S, 5S, 1'S)-5-(t-butylaminocarbonyl)amino-4-hydroxy-N-(d, 1, 7) : (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-(a) (a) 1.60 (a) 10 (cf. ca.) (x!) : hexanamide.

The compound of Example 67(a): (0.033£g, 0.05 mmol) was stirred in dry THF (0.25 mL) and tetrabutylammonium flouride (0.25 mL, 0.25 mmol) in THF was added: After 18 h.at 50°C the reaction was cooled, diluted with ethyl acetate (25 mL), washed with water (5 mL), and dried (MgSO4) in The combined organic extracts were filtered and concentrated in vacuo. 10 Chromatography (silica, 1:1 ethyl:acetate:hexane) gave the title compound as a white solid (0.018 g, 66%) (MM 226°C (dec); NMR(CD3OD)  $\delta$  7.37-6.90 (10H, m)  $\epsilon$  6.90 (2H,  $\epsilon$ ), 4.58  $\epsilon$ (1H, d, J=9 Hz), 3.71 (1H, t, J=7 Hz), 3.52 (1H, d, J=9 Hz), 2.75 (4H, m), 2.53 (1H, dd, J=4; Hz/; 12; Hz); 2.03 ((1H, m), 1.76 (1H, m), 1.66 (1H, m), 1.22 (9H, s), 0.79 (3H, d, J=7 Hz), 0.67 (3H, d, J=7 Hz); MS(ES) m/e 534 [M+H] $^+$ .

# Example 68 to To lixing and the second section of the sectio

Preparation of (2R.4S.5S.1'S)-5-(methylaminocarbonyl)amino-4-hvdroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexanamide.

Following the procedure of Examples 67(a)-67(b), except substituting methyl isocyanate for t-butylisocyanate, the = 25 title compound was prepared (0.075 mg, 51%) .sitMp 253°C ((dec); NMR (DMSOd<sup>6</sup>) 87.78 (1H, d, J=9\_Hz), 7.80-6.96 (11H, m), 6.88 (2H, S), 5.78 (1H, d, J=5 Hz), 5/72 (1H, d, J=9 Hz), 4.84 (1H, d, J=4 Hz), 4.65 (1H, m), 3.68 (1H, cq, J=7 Hz), 3.44 (1H, br), 2.74 (3H, m), 2.58 (1H, dd, J=7 Hz, 13 Hz), 2.50 30 (3H, s), 2.41 (1H, d, J=8 Hz), 1.92 5(1H, m), 1.46 (2H, m), 0.72 (3H, d, J=7 Hz), 0.63 (3H, d, J=7 Hz), MS(ES) m/e 492  $[M+H]^+$ . Sept 25: 1, 2, 20 (13), 2, ...

> J. B. B. B. W. S. C. W. E.-E. Example 69, agyer a treest 28 3, 10 12 (2, (85) 28 14 (m

> > Secretary and the second of th

Preparation of (2R.4S.5S.1'S)-5-(phenylaminocarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-: () phenylmethyl-hexamide.

Following the procedure of Examples 67(a)-67(b), except substituting phenyl isocyanate for t-butylisocyonate, the title compound was prepared (87 mg, 79%). Mp 273°C (dec); NMR(DMSO-d6), 8.50 (1H; s), 7.81 (1H, d, J=9 Hz), 7.34-6.83 (18H, m), 6.07 (1H, d, J=9 Hz), 4.99 (1H, d, J=4 Hz), 4.65 (1H, t, J=8 Hz), 3.75 (1H, m), 3.52 (1H, br), 2.77 (3H, m),

m), 0.68 (3H, d, J=7 Hz), 0.61 (3H, d, J=7 Hz); MS (DCI/NH3)
m/e 554.3; [M+H] +...

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(: 2R.4S.5S.1'S)-5-N-(propylaminocarbonyl)amino-4-hydroxy-N-

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#### 15 hexamide.

Following the procedure of Examples 67(a), except substituting n-propyl isocyanate for t-butylisocyanate, the title compound was prepared (0.048 g, 54%). Mp 247-9°C (dec); NMR(DMSO-d6) & 7.75 (1H, d, J=8 Hz), 7.23-6.94 (11H, 20 m), 6.85 (2H, s), 5.87 (1H, t, J=5 Hz), 5.65 (1H, d, J=9 Hz), 4.82 (1H, d, J=4 Hz), 4.64 (1H, t, J=8 Hz), 3.66 (1H, m), 3.38 (1H, br), 2.87 (2H, q, J=6 Hz), 2.74 (3H, m), 2.56 (1H, dd, J=7 Hz, 13 Hz), 2.39 (1H, d, J=7 Hz), 1.91 (1H, m), 1.43 (2H, m), 1.28 (2H, q, J=7 Hz), 0.77 (3H, t, J=7 Hz), 0.71 (3H, d, J=7 Hz), 0.62 (3H, d, J=7 Hz); MS(CI) m/e 520.2 [M+H]<sup>+</sup>.

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(b) 0°2 Following the method of Example 67 (a) -67 (b), except (b) dusing n-propyl thioisocyanate, the title compound was (prepared (0.012 g, 21%). Mp. 195-7°C (dec); NMR (CD3OD) & (11, 12, 132-6.86 (12H, 1m), 4.59 (1H, m), 3.64 (1H, br), 3.34 (2H, br), 2.79 (5H, m), 2.03 (1H, m), 1.73 (1H, m), 1.58 (3H, m),

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0.92 (3H, t, J=7Hz), 0.83 (3H, d, J=7Hz), 0, 68 (3H, d, J=7 Hz); MS (CI) m/e 536.2 [M+H]+.1 y and period a decay in the management of the

Example 72.8 (35-58.09) 2.54

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Preparation of (2R.4S.5S.1'S)-5-(isopropylaminocarbonyl)amino-4-hydroxy-N- (1'-isopropyl-1'-imidazol-2-yl)methyl-6-

Following the method of Example 67(a)-67(b), except substituting isopropyl isocyanate for t-butyl isocyanate, the title compound was prepared (0.034g, 46%). NMR(DMSO-d6)  $\delta$ 7.78 (1H, d, J=8 Hz), 7.24-6.97 (11H, m), 6.85 (2H, s), 5.74 (1H, d, J=8 Hz), 5.57 (1H, d, J=9-Hz), 4.83 (1H, d, J=4 Hz), 4.66 (1H, d, J=7 Hz), 3.62 (2H, m), 3.43 (1H, br), 2.73 (3H, 15 m), 2.57 (1H, dd, J=7 Hz, 13.5 Hz), 2.41 (1H, d, J=7 Hz), 1.91 (1H, m), 1.45 (2H, m), 0.95 (3H, d; J=6.5 Hz), 0.93 (3H, d, J=6.5 Hz), 0.72 (3H, d, J=6.5 Hz), 0.63 (3H, d, J=6.5 Hz); MS (CI) m/e: 520.2 [M+H]+. W Me vg the bushes on widli:

Example 73 vs (BS) (E.B v. :

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Preparation of (2R.4S.5S.1'S)-5-(aminocarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-Car on the Car on the phenylmethyl-hexamide

The compound of Example 67(a) (0.050 g; 0.094 mmol) was dissolved in triflouroacetic acid (2 mL) and stirred at 50°C for 2 h. After cooling, the reaction mixture was poured into saturated sodium bicarbonate solution (50 mL) and was extracted into ethyl acetate (100 mL). The organic solution was washed with brine, dried (MgSO4) and the solvent removed under reduced pressure. Chromatography of the residue (silica, 19:1 dichloromethane:methanol) gave the title compound as a white solid (0.036 g, 80%) ... Mp 235°C (dec); NMR (DMSO) δ.7.82 (1H, d), 7.30-6.90 (11H, m), 6.85 (2H, d), 35 5.88 (1H, m), 4.86 (1H, d), 4.67 (1H, t), 3.67 (1H, m), 3.45 (1H, m), 2.75 (3H, m), 2.60 (1H, m), 2.43 (1H, m), 1.94 (1H, m), 1, 49 (2H, m), 0.73 (3H, d), 0.62 (3H, d); MS (CI) m/e 478 [M+H]+.

Most are a constitution of the Example 74.

Preparation of (2R.4S.5S.1'S)-5-(6-ouinolinvlmethyloxy-

\ 5 (carbonyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-

: vi) wethyl-6-phenylmethyl-hexanamide

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Using the procedure of Example 34, except substituting (17 (82) (6-quinolinylmethyl) - (4-nitrophenyl) carbonate for (4-.. @ : picolinyl)-(4-nitrophenyl) carbonate, the title compound was 10 prepared.

#### Example 75

n. Preparation of (2R.4S.5S.1'S)-5-(benzovl) amino-4-hydroxy-N-

15 /11-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl- : hexanamide 能能 医多二氏性的 類 医皮肤炎的

% #10 ed a).e(2R, 4S, 5S, 11S) =5=benzoyl) amino=4=t= ...

the butyldimethylsiloxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-

(C) 0 5 (a The compound; of: Example 13(a) (0.11 g, 0.2 mmol),

., (b), at benzoyl, chloride ((0.025ag, (2.2 mmol) and (1.5 c)), (a)

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bdi(isopropyl)ethylamine (0.026 g, 0.2 mmol) were stirred together in dichloromethane (4 mL) at ambient temperature for

25 48hr. The solvent was removed under reduced pressure and the residue chromatographed (silica, 1:1 ethyl acetate:hexane) to yield the title compound as a white solid (0.080 g, 61%).

. - minimid NMR (CDCl<sub>3</sub>) 7.53 (2H, d), 7.40-7.04 (11H, m), 6.93 (2H, d),

6.69 (2H, s), 6.59 (1H, d), 6.37 (1H, d), 4.54 (2H, m), 3.68

30 (1H, t), 2.78 (2H, m), 2.66 (2H, m), 2.39 (1H, dd), 2.13 (1H,

tender dm), 1.625 (2H, t), 0.87 (9H, s), 0.53 (3H, d), 0.48 (3H, d),

add = 0.02. (3H, s), 0.00. (3H, s).

1988 64 . A. July & Con words a new box of the case of the 235. b) (2R, 4S, 5S, 1'S) -5- (benzoyl) amino-4-hydroxy-N-(1'-

: (:35 : isopropyl-1!-imidazol-2-yl) methyl-6-phenylmethyl-hexanamide

Was .1 . Character The compound of Example 75 (a) (0.080 g. 0.12 mmol) was

WE, Sh dissolved in THF (1 mL) and to this was added tetrabutylammomium fluoride, 0.16 mL, 0.16 mmol, 1M solution in THF).

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After stirring at 40°C for 24 hr, the solvent was removed under reduced pressure and the residue was chromatographed (silica, step gradient, 1:1 ethyl acetate:hexane, 9:9:2 ethyl acetate:hexane:methanol) to give the title compound as a . 5 white solid (0.051 g, 79%). Mp 253-6°C; NMR (DMSO-d<sub>6</sub>) δ 7.99 (1H, d), 7.91 (1H, d), 7.72 (2H, d), 7.50-7.02 (13H, m), 6.94 (2H, s), 4.83 (1H, br), 4.68 (1H, d), 4.14 (1H, m), 3.58 (1H, d), 2.82 (4H, m), 2.49 (1H, m), 1.92 (1H, m), 1.73 (1H, t), (1.40 (1H, m), 0.73 (3H, d); 0.63 (3H, d); MS (ES) m/e 539.2  $[M+H]^{+}$ .

#### Example 76

Preparation of (2R.4S.5S.1'S)-5-(2-furylcarbonyl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-) phenylmethyl-hexanamide andrat accept

Following the procedure of Example 75(a), except using furoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (0.019 g; 18%). Mp 212-3°C (dec); NMR(CDCl3/CD30D). \( \delta\_3 \), \( \delta\_1 \), \( \delta\_2 \), \( \delta\_3 \ (12H, m), 6.85 (2H, s), 6.49 (1H, m), 4.48 (1H, d), 4.20 (1H, m), 3.67 (1H, m), 2.96 (4H, m), 2.77% (2H, m), 12.58% (1H, d), 2.07 (1H, m), 1.71 (2H, m), 0.74 (3H, d), 0.65 (3H, d); MS(ES) m/e 528.32 [M+H]+.3 (discontentional of results for

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Preparation of (2R.4S.5S.1'S)-5-(4-methoxybenzovl)amino-4hydroxy-N-(1'-isopropyl-1'-imidazol-2-v1)methyl-6phenylmethyl-hexanamide (

Following the procedure of Example 75(a), except using 4-methoxybenzoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (32%). Mp 235-7°C (dec); NMR(CDCl<sub>3</sub>/CD<sub>3</sub>OD)  $\delta$  7:64:(2H, 4:d), 7.22-6.87 (14H, m), 6.80 (2H, m), 4.52 (1H, d); 4:16 (1H, m), 3.81 (3H, s), 3.62 (1H, d), 2.92 (2H, d), 2.72 (2H, m), 2.53 (1H, dd), 1.98 (1H, m), 1.73 (1H, m), 1.63 (1H; m), 0.71 (3H; d), i0.62 (3H, 

# Type - Later of Example 78

Preparation of (2R.4S.5S.1'S)-5-benzylcarbonyl)amino-42E 5 (hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexamide.

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In an importance the (it in an ignoral results in the

a) (2R,4S,5S,1'S)-5-benzylcarbonyl) amino-4-t-butyldimethyl
siloxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenylmethyl
10 -hexanamide.com

sphenylacetyl chloride in place of benzoyl chloride and triethylamine in place of di(isopropyl)ethylamine, the title

compound was prepared as a white solid (20%). NMR(CDCl<sub>3</sub>) δ

15.7.40-6.75 (19H, m), 5.40 (1H, d), 4.73 (1H, t), 4.41 (1H, q),

18.3.68 (1H, m), 3.48 (2H, s), 2.96 (1H, dd), 2.69 (1H, m), 2.49

(4H, m), 1.61 (2H, m), 0.92 (6H, t), 0.77 (9H, s), 0.04 (3H, s), 0.00 (3H, s).

## Example 79

### 135. applied to the control of t

The compound of Example 13(a) (0.11 g, 0.2 mmol) was dissolved in dichloromethane (2 mL), and BOP reagent (0.089 g, 0.2 mmol), triethylamine (0.028 mL, 0.2 mmol) and 4-acetoxybenzoic acid (0.043 g, 0.24 mmol) were added. After stirring at ambient temperature overnight the solvent was removed under reduced pressure. The residue was chromatographed (silica, 49:1 dichloromethane methanol) to give the title compound as a white solid (0.11 g, 78%).

NMR(CDCl<sub>3</sub>) & 7.53 (2H, d), 7.28-6.97 (13H, m), 6.83 (1H, d), 6.78 (2H, s), 6.44 (1H, d), 4.54 (2H, m), 3.72 (1H, dd), 2.79 (4H, m), 2.49 (1H, dd), 2.24 (3H, s), 2.20 (1H, m), 1.70 (2H, m), 0.91 (9H, s), 0.66 (3H, d), 0.57 (3H, d), 0.07 (3H, s), 0.02 (3H, s).

A tent by a from a

b) (2R, 4S, 5S, 1°S) -5-(4-hydroxybenzoyl) amino-4-t-butyl
-20) dimethylsiloxy-N-(1°-isopropyl-1°-imidazol-2-yl) methyl-6phenylmethyl-hexanamide \*\* Sy-2-social bake to be property

The product from reaction 79(a) (0.11 g, 0.15 mmol) was dissolved in methanol (5 mL) and powdered potassium carbonate (0.12 g, 0.9 mmol) was added. After stirring the suspension vigorously for 2 h, the mixture was filtered and the solvent removed from the filtrate at reduced pressure. Chromatography of the residue (silica, 19:19:2 ethyl acetate:hexane:methanol) gave the title compound as a white solid (0.066 g, 66%). NMR(CDCl3) & 7.35 (2H, d), 7.24-6.98 (12H, m), 6.67 (4H, m), 6.32 (1H, d), 4.63 (2H, m), 3.76 (1H, dd), 2.78 (4H, m), 2.44 (1H, d), 2.12 (1H, m), 1.64 (2H, m), 0.88 (9H, s), 0.44 (3H, d), 0.32 (3H, d), 0.05 (3H, s), 0.01 (3H, s).

35 c) (2R,4S,5S,1'S)-5-(4-hydroxybenzoyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide

Following the procedure of Example 75(b); except using the compound of Example 79(b) in place of the compound of

Example 75(a), the title compound was prepared as a white solid (57%). Mp 267-8°C (dec); NMR(CDCl<sub>3</sub>/CD<sub>3</sub>OD)  $\delta$  7.57 (2H, (1H, m), 7.33-6.75 (17H, m), 4.48 (1H, d), 4.14 (1H, m), 3.58 (1H, d), 2.90 (2H, m), 2.82 (1H, m), 2.73 (1H, m), 2.53 (1H, dd), 5 2.04 (1H, m), 1.65 (2H, m), 0.73 (3H, d), 0.58 (3H, d); MS  $(ES) m/e 555.2 [M+H]^+$ 

#### Example 80

Preparation of (2R.4S.5S.1'S)-5-(cinnamov1)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-

- been hexanamide to the first the second

Following the procedure of Example 75(a), except using cinnamoyl chloride in place of benzoyl chloride, the title 15 compound was prepared as a white solid (25%). Mp 273°C; NMR (CDCl<sub>3</sub>/CD<sub>3</sub>OD)  $\delta$  7.55-6.91 (19H, m), 6.86 (2H, s), 6.53 (1H, d), 4.37 (1H, d), 4.15 (1H, dt), 3.62 (1H, d), 2.91 (2H, m), (1.2.78 (2H, m), 2.59; (1H, dd), 2.04 (1H, m), 1.76 (1H, m), 1.65 (1H, m), 0.79 (3H, d), 0.69 (3H, d); MS: (ES) m/e 565.2 by 20 m [M+H]+. (10 m to 10 , may 2)

State of the Control of the Control and district the plant of the same (in Example 81 )

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sular Preparation of (2R.4S.5S.1'S)-5-(2-hydroxybenzovl) amino-4-25 :-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6- . The phenylmethyl-hexanamide for the second care was a state of

rd , 1875 0 Following the procedure of Example 79(a), except using GERS (2-acetoxybenzoic acid in place of 4-acetoxybenzoic acid, the title compound was prepared (50%). Mp 197°C; NMR (CD3OD) δ

30 7.77 (1H, d), 7.42-6.78 (17H, m), 4.62 (1H, d), 4.32 (1H, -6-60000 (dt), 3.71 (1H, m), 2.94 (2H, m), 2.78 (2H, m), 2.57 (1H, m), 2.03 (1H, m), 1.84 (1H, m), 1.67 (1H, m), 0.82 (3H, d), 0.68 (3H, d); MS (ES), m/e 555.2 [M+H]<sup>+</sup>.

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## and the Example 82 (a) it is a quantity

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Preparation of (2R.4S.5S.1'S)-5-(imidazoyl-4-yl-acetyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6phenylmethyl-hexanamide (1.11) (1.11) (1.11)

Following the procedure of Example 79(a) -79(c), except using (imidazol-4-yl) acetic acid in place of 4-acetoxy benzoic acid, the title compound was prepared.

Fig. 1- d Example 83 Linus 1 1500 and 10

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Preparation of (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4hydroxy-N-[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamiden and is

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a) (1S) 1-carbobenzyloxyamino-1-isopropyl-1-[(42)(E-carbomethoxyethylene)imidazol-2-yl)]methane (6.42)

The compound of Example 27(b) (100 mg, 0.33 mmol),
lithium chloride (28 mg, 0.66 mmol) and
trimethylphosphonoacetate (61 mg, 0.33 mmol) were dissolved
in anhydrous acetonitrile (2 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (55 mg, 0.36 mmol) was added and the reaction
mixture was stirred at room temperature overnight. The
solvent was removed under reduced pressure and the residue
was purified by flash chromatography (silicaa, 2% methanol/
dichloromethane to afford the title compound (72 mg, 61%).
NMR(CDCl3) & 7.60-7.10 (6H, m), 6.50 (1H, br s), 6.10 (1H, br
s), 5.15-4.95 (2H, m), 4.50 (1H, br m), 3.75 (3H, s), 2.30
(1H, br m), 1.10-0.80 (6H, m); MS m/e 358:22 (M+H)+3.7

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b) (1S)-1-amino-1-isopropyl-1-(4-carbomethoxyethylimidazol-2-yl)methane

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Following the procedure of Example 1(b), except substituting the compound of Example 82(a) for the compound of Example 1(a), the title compound was prepared. NMR(CDCl3) 8 6.65 (1H, s), 4.40 (2H, br s), 3.82 (1H, d, J=3 Hz), 3.65 (3H, s), 2.90-2.55 (4H, m), 2.05 (1H, m), 0.90 (6H, d, J=3Hz).

- c) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-butyldimethylsiloxy-N-[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2yl)]methyl-6-phenyl-2-phenylmethyl-hexanamide
- 5 Following the procedure of Example 1(c) except using the compound of Example 82(b), the title compound was prepared. NMR(CDCl3) δ 7.35-6.90 (12H, m), 6.55 (1H, s), 4.75 (1H, d, J=4 Hz), 4.45 (1H, m) 3.95 (1H, m), 3.70 (3H, s), 2.90-2.40 (9H, m), 1.90-1.60 (2H, m), 1.38 (9H, s), 10 0.90-0.70 (15H, m), 0.10 (6H, d, J=2 Hz).
- d) (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N[1'-isopropyl-1'-(4-carbomethoxyethylimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide.
- Following the procedure of Example of 9(d) except using the compound of Example 83(c), the title compound was prepared. NMR(CDCl3) δ 7.30-6.90 (10H, m), 6.55 (1H, s), 5.00 (1H, d, J=4 Hz), 4.45 (1H, m), 3.70 (3H, s), 2.95-2.50 (9H, m), 2.25 (1H, m), 1.80-1.60 (2H, m), 0.85 (9H, s), 0.70 (6H, d, J=3 Hz); MS m/e 621.4 [M+H]<sup>+</sup>.

## Example 84

Preparation of (2R.4S.5S.1'S)-5-(t-butoxycarbonyl)amino-425 hydroxy-N-[1'-isopropyl-1'-(4-carboxamidoimidazol-2yl) lmethyl-6-phenyl-2-phenylmethyl-hexanamide

(18)-1-carbobenzyloxyamino-1-isopropyl-1-[(4-(hydrazinocarbonyl)imidazol-2-yl)]methane

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Anhydrous hydrazine (47 μL, 1.5 mmol) was added to a solution of the compound of Example 26(b) (100 mg, 0.30 mmol) in anhydrous methanol. The resulting mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 10% aqueous Na<sub>2</sub>CO<sub>3</sub> and the organic extract was dried over Na<sub>2</sub>CO<sub>3</sub> and evaporated under reduced pressure. The residue was purified by flash chromatography (silica, 4% methanol/dichloromethane) to afford the title compound (52)

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mg, 52%). NMR(CD<sub>3</sub>OD) δ 7.50 (1H, s), 7.30-7.20 (5H, m), 5.00-4.90 (2H, m), 4.45 (1H, d, J=6 Hz), 2.10 (1H, br m), 0.95-0.75 (6H, m); MS m/e 332.2 [M+H]<sup>+</sup>

b) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-[(4azidocarbonyl)imidazol-2-yl]methane

The compound of Example 83(a) was dissolved in 2N HCl (1 mL) and glacial acetic acid (0.2 mL) and cooled in an ice bath. A solution of sodium nitrite (11 mg, 0.16 mmol) in H2O (200 μL) was added dropwise. The reaction mixture was stirred for 0.5 h, neutralized with cold concentrated ammonium hydroxide and extracted with ethyl acetate. The organic extract was dried over Na2CO3 and the solvent removed in vacuo to yield the title compound (54mg. 100%). NMR(CDCl3) δ 7.75 (1H, s), 7.35-7.20 (5H, m), 5.20-5.00 (2H, m), 4.62 (1H, br m), 2.60 (1H br m), 1.10-0.80 (6H, m); IR 2123cm-1 (CON3).

c) (1S)-1-carbobenzyloxyamino-1-isopropyl-1-(4-(1-1)) carboxamidoimidazol-2-yl)methane

The compound of Example 83(b) was dissolved in 2 mL of ethyl acetate and stirred with of concentrated ammonium hydroxide (1 mL) at 0°C for 0.5 h, then at room temperature overnight. The reaction mixture was diluted with H2O, extracted with ethyl acetate, and dried over Na<sub>2</sub>CO<sub>3</sub>. The solvent was removed in vacuo and the residue was purified by flash chromatography (silica, 4% methanol/ dichloromethane) to afford the title compound (50mg, 100%). NMR(CDCl<sub>3</sub>) & 7.45 (1H; s), 7.25-7.10 (5H, m), 5.00-4.85 (2H, m), 4.35 (1H, d, J=3 Hz), 2.00 (1H, br m), 0.90-0.70 (6H, m); MS m/e 317.2 [M+H]<sup>+</sup>.

d) (1S)-1-amino-1-isopropyl-1-(4-carboxamidoimidazol-2-yl) methane.

Following the procedure of Example 1(b), except substituting the compound of Example 83(c) for the compound of Example 1(a), the title compound was prepared. NMR(CDCl3)

5 (1H, s), 3.47 (1H, d, J=3 Hz), 1.80 (1H, br m), 0.75the transfer was a realist

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.... e). (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-t-5 butyldimethylsiloxy-N-[1'-isopropyl-1'-(4carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-

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recover and therefore a large con-

Following the procedure of Example 1(c), except using the compound of Example 83(d), the title compound was 10 prepared. NMR (CDCl3) δ 7.50 (1H, s), 7.45-6.90 (11H, m), effet 6.25 (1H, d, J=4 Hz), 4.50 (1H, d, J=6Hz), 4.10 (1H, br.m), (11) 3.60 (1H, m), 2.90-2.40 (5H, m), 1.90 (1H, br m), 1.70-1.50 (2H, br.m), 1.35 (9H, s), 0.90 (9H, s), 0.70-0.60 (6H, m),

f) (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-carboxamidoimidazol-2-yl)]methyl-6phenyl-2-phenylmethyl-hexanamide

Following the procedure of Example 9(d) except using the 20 compound of Example 83(e) the title compound was prepared.  $\Sigma_{0}$  NMR (CD3OD)  $\delta$  7.45 (1H, s), 7.25-6.85 (1OH, m), 4.50 (1H, d,  $(\text{fine}; \sqrt{3}, \text{J-6,Hz}), \sqrt{4.10}, (\text{1H, m}), 3.60, (\text{1H, m}), 2.85-2.50, (\text{5H, m}), 2.00$ (1H, (br m), 1.80-1.50 (2H, m), 1.30 (9H, s), 0.80-0.65 (6H, m); MS m/e, 578.2 [M+H] +.

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Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-vl))methyl-hexanamide

a) (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-t-butyldimethyl-siloxy-5-\_thioureido-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-W. Whexanamide out (1 is the limit .- is to record to the Block (2 costs).

A solution of benzoyl isothiocyanate (prepared from 35 ammonium thiocyanate (147 mg, 1.93 mmol); and benzoyl chloride (257 mg, 1.84 mmol) in of acetone (10 mL) according to the

procedure of J. Amer. Chem. Soc., 56, 1408 (1934)) was treated with a solution of (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-tbutyldimethylsiloxy-5-amino-6-phenyl-N-(1)-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide (1.0 g, 1.83 mmol) in acetone. After 20 min at 23°C, the solvent was evaporated, and the residue was dissolved in diethyl ether. The ether extract was washed with water, dried, and the solvent was evaporated. This residue was dissolved in of MeOH (25 mL), treated with 2.5N NaOH (0.1 mL) and heated to 50°C for 30 min. The solvent was evaporated, and the residue was dissolved in EtOAc. The organic solution was washed with water, dried, and the solvent evaporated. The residue was chromatographed (silica, 5% MeOH/CHCl3) to yield the title compound (520 mg, 47%). NMR (DMSÓ)  $\delta \cdot 7.80^{\circ} (1H_{\nu}) d) + 7.35 (1H_{\nu}) d$ d), 6.70-7.20 (15H, m), 4.69 (1H, t), 4.54 (1H, m), 3.78 (1H, m), 2.72-2.86 (3H, m), 2.54 (1h, dd), 2:42 (1H, dd), 2.04 (1H, m), 1.82 (1H, m), 1.30 (1H, m), 0.92 (9H, s), 0.86 (3H, d), 0.74 (3H, d), 0.15 (6H, d). (31, 88, 88, 88) complete to a control of the transport of the transport of the

20 b) dimethylformamidino derivative of (2R, 4S, 5S, 1'S)-2phenylmethyl-4-dimethyl-t-butyl silyloxy-5-thioureido-6phenyl-N-(1'-isopropyl-1'-(imidazo-2-yi)) methyl-hexanamide

A solution of the compound of Example 85(a) (122 mg, 0.2 mmol) and dimethylformamide dimethylacetal (26 mg, 0.22 mmol) in CHCl<sub>3</sub> (2 mL) was stirred at 23°C for 16 h. The solvent and excess reactant was removed under high vacuum, and the residue was chromatographed (Florisil®, 2\* MeOH/CHCL<sub>3</sub>) to yield the title compound (100 mg, 76\*). NMR(CDCl<sub>3</sub>) & 8.82 (1H, s), 7.05-7.40 (12H, m), 6.76 (1H, br s), 6.60 (1H, d), 3.14 (3H, s),

5.32 (1H, m), 4.66 (1H, dd), 3.88 (1H, dd), 3.14 (3H, s),
3.05 (3H, s), 2.70-3.04 (4H, m), 2.40 (2H, m), 1.68 (2H, m),
1.00 (9H, s), 0.80 (6H, dd), 0.14 (6H, d).

c). (2R,4S, 5S, 1'S)-2-phenylmethyl-4-dimethyl-t-butyl
silyloxy-5-(5-(1-oxopropyl)-2-thiazolyl)amino) 6-phenyl-N(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

A solution of the compound of Example 85(b) (100 mg, 0.15 mmol), 1-bromo-2-butanone (25 mg, 0.165 mmol), and

triethylamine (33 mg, 0.165 mmol) in acetonitrile (10 mL) was heated at 80°C for 3.5 h. The solvent was evaporated, and the residue shaken with a mixture of diethyl ether and aqueous NaHCO3. The ether was seperated, washed with water, 5.8 dried, and the solvent was evaporated. The residue was recrystallized from a mixture of CHCl3 and hexane to yield the title compound (59 mg, 57%). NMR(CDCl3) & 7.75 (1H, s), 67.02-7.385(10H, m), 6.881(2H, m), 6.80 (1H, br s), 6.70 (1H, c) (2.82 (3H, m), 2.72 (2H, q), 2.54 (2H, m), 2.20 (1H, m), 2.04 (1H, m), 1.66 (1H, m), 1.15 (3H, t), 0.96 (9H, s), 0.72 (6H, t), 0.10 (6H, d).

(2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(5-(1-

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oxopropyl)-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'(imidazo-2-yl))methyl-hexanamide

A solution of the compound of Example 85(c) (50 mg, 0.07 mmol) in (2 mL) of THF was treated with) of tetrabutyl-ammonium fluoride (0.2 mL, 1N solution in THF) 58°C for 1 h.

- The solvents were evaporated, and the residue dissolved in ether. The ether was washed with water, dried, and the solvent evaporated. The residue was chromatographed (neutral alumina, Activity, V, impurities removed with 2% MeOH/EtOAc, product eluted with 5% MeOH/CHCl3) to yield the title
- 25 compound (22 mg, 55%). NMR (DMSO) & 7.75 (1H, s), 7.66 (1H, d), 6.80-7.30 (13H, m), 4.93 (1H, br s), 4.78 (1H, t), 3.78 (1H, m), 3.68 (1H, dd), 3.00 (1H, dd), 2.92 (1H, dd), 2.86 (1H, m), 2.80-2.90 (1H, br), 2.76 (2H, q), 2.56 (2H, m), 2.12 (1H, m), 1.74 (1H, m), 1.69 (1H, m), 1.20 (3H, t), 0.80 (3H, 30 d), 0.73 (3H, d)

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#### Example 86

Preparation of (2R,4S,5S,1'S)=2-phenylmethyl-4-hydroxy-5-(5-35 (1-oxopropyl)-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

1.

a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-dimethyl-t-butyl silyloxy-5-(2-thiazolylamino) -6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide.

The compound of Example 85(a) (50 mg, 0.08 mmol) in CHCl3 (2 mL) was treated with chloroacetaldehyde (50 mg, 0.64 mmol). After 20 min the solvent and excess reagent were evaporated. The residue was dissolved in EtOAc, washed with aqueous NaHCO3, dried and the solvent evaporated. The residue was chromatographed (Florisil®, 60% EtOAc/hexane) to yield the title compound (42 mg, 83%). NMR(CDCl3) & 7.12-7.30 (10H, m), 7.02 (1H, d), 6.92 (2H, m), 6.82 (1H, br), 6.62 (1H, br), 6.38 (1H, d), 5.86 (1H, br), 4.58 (1H, t), 4.00 (1H, m), 3.86 (1H, m), 2.85 (3H, m), 2.52 (2H, m), 2.26 (1H, m), 2.16 (1H, m), 1.68 (1H, m), 0.98 (9H, s), 0.70 (6H, t), 0.12 (6H, d).

b) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-coxopropyl)-2-thiazolyl) amino) -6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl)) methyl-hexanamide

Following the procedure of Example 85(d), except substituting the compound of Example 86(a) for the compound of Example 85(c), the title compound was prepared.

NMR(CDCl<sub>3</sub>/DMSO) & 6.80-7.42 (14H, m); 6.40 (2H, m); 5.18 (1H, br), 4.74 (1H, t), 3.70 (1H, m), 3.62 (1H, m), 3.00 (2H, m), 2.88 (2H, m), 2.58 (1H, m), 2.18 (1H, m), 1.80 (2H, m), 1.72 (6H, dd).

Example 87 ( 1900.0 (6 357)

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- Preparation of (2R.4S.5S.1'S)-2-phenylmethyl-4-hydroxy-5-(5-propyl-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide
- a) (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-t-butyldimethylsilyloxy-5-35/ (5-propyl-2-thiazolyl)amino) -6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide

A solution of the compound of Example 85(a) (120 mg, 0.2 mmol) in CHCl<sub>3</sub> (5 mL) was treated with 2-bromovaleraldehyde

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(100 mg, 0.6 mmol) and warmed to 60°C for 30 min and 80°C for 5 min. The solvent and excess reagent were removed under reduced pressure. The residue was dissolved in EtOAc, washed with aqueous K2CO3, dried, and the solvent evaporated. The residue was chromatographed (silica, 3% MeOH/CHCl3) to yield the title compound (55 mg, 41%). NMR(CDCl3) & 7.10-7.30 (10H, m), 6.88 (2H, m), 6.72 (1H, br), 6.68 (1H, s), 6.60 (1H, br), 5.60 (1H, br), 4.62 (1H, t), 3.94 (1H, m), 3.78 (1H, t), 2.82 (3H, m), 2.50 (4H, m), 2.26 (1H, m), 2.04 (1H, m), 1.66 (1H, m), 1.55 (2H, sextet), 0.94 (9H, s), 0.92 (3H, t), 0.70 (6H, dd), 0.08 (6H, d).

b). (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(5-propyl-2-thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide.

Following the procedure of Example 85(d), except substituting the compound of Example 87(a) for the compound of Example 85(c), the title compound was prepared. NMR(CDCl<sub>3</sub>) δ 7.50 (1H, br), 6.90-7.24 (10H, m), 6.78 (2H, s), 6.60 (1H, s), 6.18 (1H, br), 5.76 (1H, br), 4.60 (1H, t), 3.68 (1H, m), 3.52 (1H, m), 3.05 (1H, dd), 2.95 (2H, m), 2.82 (1H, dd), 2.62 (1H, m), 2.58 (2H, t), 2.32 (1H, m), 1.86 (2H, m), 1.60 (2H, sextet), 0.96 (6H, t), 0.75 (6H, dd).

#### 25 <u>Example 88</u>

Preparation of (2R.4S.5S.1'S)-5-(nicotinyl)amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide

Following the procedure of Example 75(a), except using nicotinoyl chloride in place of benzoyl chloride, the title compound was prepared as a white solid (43%). Mp 233-4°C (dec); NMR(CDCl<sub>3</sub>/CD<sub>3</sub>OD) & 8.81 (1H, d), 8.59 (1H, dd), 7.99 (1H, m), 7.35-6.86 (14H, m), 6.79 (2H, s), 4.44 (1H, d), 4.19 (1H, dt), 3.59 (1H, m), 2.90 (2H, d), 2.68 (2H, m), 2.52 (2H, m), 1.96 (1H, m), 1.71 (1H, m), 1.58 (1H, m), 0.70 (3H, d), 0.58 (3H, d); MS(ES) m/e 540.2 [M+H]+.

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The above description fully discloses how to make and
            1997 use the present invention. However, the present dinvention is
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   the scope of the following claims to good the subject of
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wherein: [ (C-1) ... )

R<sup>1</sup> and R<sup>3</sup> are each independently Q, Q-C<sub>1-6</sub>alkyl, Q-C<sub>2-6</sub>alkenyl, Q-C<sub>2-6</sub>alkynyl or C<sub>1-6</sub>alkyl substituted by one to five fluorine atoms, each optionally substituted by R<sup>23</sup>; Q is H, C<sub>3-6</sub>cycloalkyl, C<sub>5-6</sub>cycloalkenyl, Ar or Het

R<sup>2</sup> is H or OH; R<sup>4</sup> is R<sup>6</sup>-NR<sup>11</sup>- or CONR<sup>11</sup>CHR<sup>6</sup>R<sup>7</sup>; R<sup>5</sup> is R<sup>6</sup>-NR<sup>11</sup>- or R<sup>10</sup>-NR<sup>11</sup>-;

 $s = X I_{R^0}$ 

x is NR11, O or S;

 $R^7$  is Q, Q-C<sub>1-6</sub>alkyl or Q-C<sub>2-6</sub>alkenyl;

R8 and R9 are each independently H, OH, halo, NO2, COR12, CF3, Ar, C1-6alkyl-R15, or R17(R18R19C)m, or together form a

20 fused C2-4alkylene, aryl or heteroaryl moiety;

 $R^{10}$  is A-(B)<sub>n</sub>-;

 $R^{11}$  is H or  $C_{1-4}$ alkyl;

R<sup>12</sup> is R<sup>7</sup>, OR<sup>7</sup>, NR<sup>7</sup>R<sup>11</sup> or an amino acid or amino alcohol; B is an amino acid;

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G'25 The A is H, Ar, Het, R<sup>17</sup> (R<sup>18</sup>R<sup>19</sup>C), Ar-W, Het-W or R<sup>17</sup> (R<sup>18</sup>R<sup>19</sup>C), —W, or phthaloyl each optionally substituted by one to three groups chosen from R<sup>15</sup> or C<sub>1-6</sub>alkyl-R<sup>15</sup>;

W is C=0, OC (=0),  $NR^{11}C$  (=0), SC (=0),  $NR^{11}C$  (=S),  $SO_2$ ,  $R^{11}SO_2$  or P (=0)  $(OR^{22})$ ;

C=OR<sup>22</sup>, CO<sub>2</sub>R<sup>22</sup>, CON(R<sup>16</sup>)<sub>2</sub>, N(R<sup>22</sup>)<sub>2</sub>, NHC(=N)NH-A, I, Br, Cl, F, OR<sup>10</sup>, or OH, provided that when R<sup>15</sup> is a substituent of the carbon adjacent to W, R<sup>15</sup> is not halogen or OH when W is OC(=0) or NHCO;

35  $R^{16}$  is H or  $C_{1-6}$ alkyl;

R<sup>17</sup>, R<sup>18</sup> and R<sup>19</sup> are independently: i) H, R<sup>15</sup> or C<sub>1-4</sub>alkyl, C<sub>2-6</sub>alkenyl, phenyl, naphthyl, C<sub>3-6</sub>cycloalkyl or Het, each optionally substituted by one to three R<sup>15</sup> or R<sup>15</sup>-C<sub>1-6</sub>alkyl groups, or ii) R<sup>17</sup> is as above and (R<sup>18</sup>R<sup>19</sup>C) are joined together to form a phenyl, naphthyl, C<sub>3-6</sub>cycloalkyl or Het ring, or iii) R<sup>17</sup> is as above and R<sup>18</sup> and R<sup>19</sup> together are =0;

R<sup>22</sup> is H, C<sub>1-6</sub>alkyl, phenyl or phenyl-C<sub>1-4</sub>alkyl;

 $R^{23}$  is  $-X'-(CH_2)_qNR^{24}R^{25}$ ,  $X''[((CH_2)_rO)_s]R^{26}$ ,

CH2X"[((CH2)rO)s]R<sup>26</sup>, or benzofuryl, indolyl, azacycloalkyl, azabicyclo C7-11cycloalkyl or benzopiperidinyl, optionally substituted with C1-4alkyl;

g is 2-5;

s is 1-6 and r is 1-3 within each repeating unit s; X' is CH2, O, S or NH;

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; + (8) · X · 1 (6)

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X" is CH2, NR', O, S, SO or SO2;

R<sup>24</sup> and R<sup>25</sup> are i) C<sub>1-6</sub>alkyl, optionally substituted by OH, C<sub>1-3</sub>alkoxy, or N(R')<sub>2</sub>, ii) the same or different and joined together to form a 5-7 member heterocycle containing up to two additional heteroatoms selected from NR, O, S, SO, SO<sub>2</sub>, said heterocycle optionally substituted with C<sub>1-4</sub>alkyl, iii) aromatic heterocycle, optionally substituted with C<sub>1-4</sub>alkyl or N(R')<sub>2</sub>;

R' is H or C1-4alkyl;

 $R^{26}$  is H,  $C_{1-4}$ alkyl,  $C(=0)R^{27}$ ,  $C(=0)U[(CH_2)_mO]nR'$ ,  $P(=0)(OM)_2$ ,  $CO_2R^{27}$ ,  $C(=0)NR^{27}R^{28}$ , where M is a mono or divalent metal ion, and U is NR' or  $O_{12}$ .

R<sup>27</sup> is C<sub>1-6</sub>alkyl or Ar, optionally substituted with one or more hydroxy, carboxy, halo, C<sub>1-3</sub>alkoxy, CONR'2, NR'2, CO<sub>2</sub>R', SO<sub>2</sub>NR'<sub>2</sub>, CH<sub>2</sub>NR<sub>2</sub>, NR'COR', NR'SO<sub>2</sub>R', X"[(CH<sub>2</sub>)<sub>T</sub>O]<sub>S</sub>R' or CH<sub>2</sub>X"[(CH<sub>2</sub>)<sub>T</sub>O]<sub>S</sub>R';

 $R^{28}$  is H,  $C_{1-6}$ alkyl or together with  $R^{27}$  forms a 5-7 membered heterocycle or a 6 membered heterocycle containing a heteroatom selected from N, O and S;

25

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or a pharmaceutically acceptable salt thereof. 300 300

2. A compound according to claim 1 wherein:

R1 and R3 are C1-6alkyl, Ar-C1-6alkyl, Ar-C2-6alkenyl,
Ar-C2-6alkynyl, or C1-6alkyl optionally substituted by one to

R4 is CONR<sup>11</sup>CHR<sup>6</sup>R<sup>7</sup>;

R<sup>8</sup> is H, C<sub>1-6</sub>alkyl, COR<sup>12</sup>, NO<sub>2</sub> or Br;

- tync10 may and R9 is H, NO2, Br. COR12, CF3, Ar, C1-6alkyl or C1-6alkyl-R15, wherein R12 is H, C1-6alkyl, Ar, OC1-6alkyl, NH2, and R15 is OH;

-(iyika Gray ) (A.is.H., Het, R17(R18R19C)m-W or Het-W;

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15 R<sup>17</sup>, R<sup>18</sup> and R<sup>19</sup> are H, or C<sub>1-4</sub>alkyl, Het or Ar, each with optionally substituted by one or two R<sup>15</sup> or R<sup>15</sup>C<sub>1-6</sub>alkyl groups, or (R<sup>18</sup>R<sup>19</sup>C) are joined together to form a phenyl, C<sub>3-6</sub>cycloalkyl or Het ring; and when he were to the same of the same of

-: (quodingymod)W(is C=0,00C(=0)',-NHC(=0)', NHC(=S)' or SC(=0) .)

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3. A compound according to claim 1 wherein R4 is CONR<sup>11</sup>CHR<sup>6</sup>R<sup>7</sup> and X is N-H.

of Collection and the interesting an expension and the state of the collection of the state of t

- 4. A compound according to claim 3 wherein R<sup>8</sup> is H and R<sup>9</sup>
  -25 ] is H or COR<sup>12</sup>. Here two a vertical and R<sup>9</sup>
  - 5. A compound according to claim 4 wherein R7 is C1-6alkyl.

30 R<sup>3</sup> is benzyl, 4-hydroxy-benzyl or phenylpropenyl. A compound according to claim 3 wherein R<sup>1</sup> is benzyl and 30 R<sup>3</sup> is benzyl, 4-hydroxy-benzyl or phenylpropenyl.

7. (A) compound according to claim 3 wherein A is

R<sup>17</sup>(R<sup>18</sup>R<sup>19</sup>C)<sub>m</sub>-W, and R<sup>17</sup>, R<sup>18</sup> and R<sup>19</sup> are H, or C<sub>1-4</sub>alkyl, Het

- 12 or Ar. (a feet a section of the content of the con

8. A compound according to claim 3 wherein B is absent and A is C1-6alkylOC(=0).

- 9. A compound according to claim 3 wherein W is C=0.
- 10. A compound according to claim 1 wherein the compound is: (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
- amino-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide hydrochloride;

  (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-amino-6-phenyl-N-[1'-isopropyl-1'-(4-aminocarbonyl-thiazo-2-yl)]methyl-hexanamide;
- 10 (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-[1'-isopropyl-1'-(thiazo-2-yl)]methyl
  - hexanamide;
    (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl) amino-6-phenyl-N-(1'-imidazo-2-yl) methyl-hexanamide
  - hydrochloride;

    (2R, 4S, 5S, 1'S) 2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)amino-6-phenyl-N-[1'-methyl-1'-(imidazo-2-yl)]& methylhexanamide hydrochloride;

    (2R, 4S, 5S, 1'S) 2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-
  - amino-6-phenyl-N-[1'-benzyl-1'-(imidazo-2-yl)]methylhexanamide hydrochloride;
    (2R, 4S, 5S, 1'S)-5-(carbobenzyloxy)amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide;
- 25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1!-isopropyl-1'-(4, 5-dimethyl) imidazol-2-yl] methyl-6-phenyl-2
  (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(N'-methyl) imidazol-2-yl] methyl-6-phenyl-2
  - phenylmethyl-hexanamide;

    (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-(3phenylpropargyl) hexanamide;

    (2R, 4S, 5S, 1'S) -5-(isopropoxycarbonyl) amino-4-hydroxy-N-(1'-
  - 35 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl6 to hexanamide; the new part of the property of the second of the

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- (2R, 4S, 5S, 1'S) -5-(benzyloxyethoxycarbonyl) amino-4-hydroxy-N-
phenylmethyl-hexanamide;
       (2R, 4S, 5S, 1'S) -5- (methoxycarbonyl) amino-4-hydroxy-N-(1'-
i. no 5 isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
         hexanamide;
         (2R, 4S, 5S, 1'S) -5-(ethoxycarbonyl) amino-4-hydroxy-N-(1'-
      isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
         hexanamide;
   10: (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(3-phenyl-2-
        propenyl) hexanamide;
         (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
     isopropyl-1'-(4-nitroimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
    - '1 (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
     ethyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
        hexanamide:
    (2R, 4S, 5S, 1'S)-5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
   20 propyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
        hexanamide:
     (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
   isopropyl-1'-(4-bromoimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
    25 (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
  - 'gas isopropyl-1'-(4,5-dibromoimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
    - : (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
        isopropyl-1'-(4-methylimidazol-2-yl)]methyl-6-phenyl-2-
        phenylmethyl-hexanamide;
    - :: (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl);amino-4-hydroxy-N-[1'-
        isopropyl-1'-(4-trifluoromethylimidazol-2-yl)]methyl-6-
        phenyl-2-phenylmethyl-hexanamide;
       (2R, 4S, 5S, 1'S) -5- (t-butoxycarbonyl) amino-4-hydroxy-N-methyl-
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N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-

phenylmethyl-hexanamide;

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(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
     isopropyl-1'-(4-carbomethoxyimidazol-2-yl)]methyl-6-phenyl-2-
                                 on internation of the following
    phenylmethyl-hexanamide;
     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
    isopropyl-1'-(4-methylcarbonylimidazol-2-yl)]methyl-6-phenyl-
    2-phenylmethyl-hexanamide;
  (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
    isopropyl-1'-(4-isopropylcarbonyl-imidazol-2-yl)]methyl-6-
                                              The force.
    phenyl-2-phenylmethyl-hexanamide;
     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
10
    isopropyl-1'-(4-phenylcarbonyl-imidazol-2-yl)]methyl-6-
    phenyl-2-phenylmethyl-hexanamide; bickershate lives with the phenyl-
     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
    isopropyl-1'-(4-formylimidazol-2-yl)]methyl-6-phenyl-2-
                                 Commission of the Commission
    phenylmethyl-hexanamide;
15
     (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
   isopropyl-1'-(4-(hydroxymethyl)-imidazol-2-yl)]methyl-6-
    phenyl-2-phenylmethyl-hexanamide;
  (2R, 4S, 5S, 1'S)-5-((tetrahydrothiopyran-4-yl)oxycarbonyl)-
    amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
20
    phenyl-2-phenylmethyl-hexanamide;
    (2R, 4S, 5S, 1'S) -5-((tetrahydro-4H-pyran-4-yl)oxycarbonyl)-
   amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
    phenyl-2-phenylmethyl-hexanamide; and the way and the second
25 (2R, 4S, 5S, 1'S) -5-(4-picolinyloxy) amino-4-hydroxy-N-(1'-
   isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-
                                    "Managada haifbe
    hexanamide;
    (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
    isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-(4,4,4-
    trifluorobut-1-yl) hexanamide ; digum and contact and
   (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
    isopropyl-1'-(4-((1RS)-1-hydroxyethyl)-imidazol-2-yl)]methyl-
    (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-(1-
    methyl)propyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-
35
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phenylmethyl-hexanamide:

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(2R, 4S, 5S, 1'S) -5-(propylaminocarbonyl) amino-4-hydroxy-N-[1'-
                     isopropyl-1'-(imidazol-2-yl)]methyl-6-phenyl-2-phenylmethyl-
                                                                        rager with a visited.
                    hexanamide;
         ...; (2R, 4S, 5S, 1'S) -5- (4-hydroxybutanoy1) amino-4-hydroxy-N- (1'-
                    isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
                    phenylmethylhexanamide; ....
                     (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(benzyloxy-
              carbonyl)valylamino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-
                    yl) methyl-hexanamide;
      y a 10 gt (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(N-acetylvalyl) -
                   amino-6-phenyl-N-(1'-isobutyl-1'-imidazo-2-yl)methyl-
                    hexanamide;
                     (2R, 4S, 5S, 1'S) -5-[(imidazol-2-yl)methyloxycarbonyl]amino-4-
      -: x: hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl) methyl-6-phenyl-2-
                   phenylmethyl-hexanamide;
    Y - 22 (25 (2R; 4S, 5S, 1'S, 1"RS) -5- ((1"-(imidazol-2-yl)-2"-methyl) -
                   propyloxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
                    imidazol-2-yl)methyl-6-phenyl-2-phenylmethyl-hexanamide;
     (2R,4S,5S,1'S)-5-(t-butoxycarbonyl)amino-4-hydroxy-N-[1'-
     20 // isopropyl-1!-(4-(imidazol-2-yl)imidazol-2-yl)]methyl-6-
· · · i) - i - v: phenyl-2-phenylmethyl-hexanamide;
    tobro and (2R, 4S, 5S, 1'S) -5- (1-oxo-thian-4-yl) oxycarbonyl) amino-4-
        hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
         25 (2R, 4S, 5S, 1'S)-5-((tetrahydrosulfonylpyran-4-
                  yl) oxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
                  yl) methyl-6-phenyl-2-phenylmethylhexanamide;
             (2R, 4S, 5S, 1'S) -5- ((1, 1-dimethyl-2-(benzyloxycarbonyl-
   white plycyloxy) ethoxycarbonyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
      " (30 (Cimidazol-2-yl) methyl-6-phenyl-2-phenylmethyl-hexanamide
                   hydrochloride salt; has (iven the land the land to be a l
                    (2R, 4S, 5S, 1'S)-5-((1, 1-dimethyl-2-glycyloxy) ethoxycarbonyl)-
                 -amino-4-hydroxy-N-(1!-isopropyl-1!-imidazol-2-yl)methyl-6-
         aphenyl-2-phenylmethyl-hexanamidedihydrochloridesalt;
           35 c/(2R, 4S, 5S, 1'S) -5-((1-acetyl) amino-4-hydroxy-N-(1'-isopropyl-
                   1'-imidazol-2-yl)methyl-6-phenyl-2-phenylmethylhexanamide;
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(2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
             isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4-)
             benzyloxyphenylmethyl) hexanamide;
                                                                                               in obligation of
             (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-(1'-
             isopropyl-1'imidazol-2-yl)methyl-6-phenyl-2-(4-c-...
             hydroxyphenylmethyl) hexanamide; म् अवनुस्तव्य मुख्य बहुई प्रतः वर्षः
              (2R, 4S, 5S) -5-(t-butoxycarbonyl)amino-4-hydroxy-2- 1;
             phenylmethyl-6-phenyl-N-[1'-cyclopropyl-1'-imidazol-2-
                                                                            (statements tell pation )
              yl]methyl-hexanamide;
(2R, 4S, 5S, 1'S) -5-((isopropylthiol) carbonyl) -amino-4-hydroxy-
             2-phenylmethyl-6-phenyl-N-[1-isopropyl-1'-imidazol-2-
             yl]methyl-hexanamide;
              (2R, 4S, 5S, 1'S) -5-[3-(1H-imidazol-2-yl)-3-hydroxy-4-;
             methylpentylamido]-4-hydroxy-N-(1'-isopropyl-1'-imidazol-2-
             yl)methyl-6-phenyl-2-phenylmethyl-hexanamide; a sign
            (2R, 4S, 5S, 1'S) -5-[(4-methoxyphenoxy)carbonyl]amino-4-hydroxy
             N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenyl-2-
             phenylmethyl-hexanamide; p. sor . with the layes to the side
             2R, 4S, 5S, 1'S) -5-(t-butylaminocarbonyl) amino-4-hydroxy-N-(1'-
    20 isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
              (2R, 4S, 5S, 1'S)-5-(methylaminocarbonyl)-amino-4-hydroxy-N-(1'-
            · isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
              (2R, 4S, 5S, 1'S)-5-phenylaminocarbonyl) amino-4-hydroxy-N-(1'-
             isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
              (2R, 4S, 5S, 1'S) -5-N-(propylaminocarbonyl) amino-4-hydroxy-N-
     (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
                                            you be a way to great out on the great of the files
             hexamide;
              (2R, 4S, 5S, 1'S) -5-(n-propylaminothiono) amino-4-hydroxy-N-
              (1'isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
             2R, 4S, 5S, 1'S) -5-(isopropylaminocarbonyl) -amino-4-hydroxy-N-
              (1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
             hexamide; of the tensor of the property of the
             (2R, 4S, 5S, 1'S) -5- (aminocarbonyl) amino-4-hydroxy-N-(1'-
             isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
    35 (2R, 4S, 5S, 1'S) -5-(6-quinolinylmethyloxy-carbonyl)amino-4-
        hydroxy-N-(1'-isopropyl-1'-imidazol-2-yl)methyl-6-
             phenylmethyl-hexanamide;
```

```
(2R, 4S, 5S, 1'S) -5- (benzoyl) amino-4-hydroxy-N-(1'-isopropyl-1'-
         imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
          (2R, 4S, 5S, 1'S) -5- (2-furylcarbonyl) amino-4-hydroxy-N- (1'-
        isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
  5 ~ (2R, 4S, 5S, 1'S) -5-(4-methoxybenzoyl) amino-4-hydroxy-N-(1'-
         .isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
          (2R, 4S, 5S, 1'S) -5-benzylcarbonyl) amino-4-hydroxy-N-(1'-
      maraisopropyl-1!-imidazol-2-yl)methyl-6-phenylmethyl-hexamide;
      (2R, 4S, 5S, 1'S) -5- (4-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S) -5- (cinnamoyl) amino-4-hydroxy-N-(1'-isopropyl-
     1. imidazol-2-yl) methyl-6-phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S) -5- (2-hydroxybenzoyl) amino-4-hydroxy-N-(1'-
         isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-hexanamide;
VIH :150 (2R, 4S, 5S, 1'S)-5-(imidazoyl-4-yl-acetyl)amino-4-hydroxy-N-
 . ..o Jun(1'-isopropyl-1'-imidazol-2-yl)methyl-6-phenylmethyl-
         hexanamide:
                               and the second of the second
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
      en isopropyl-17-(4-carbomethoxyethylimidazol-2-yl)]methyl-6-
    20 phenyl-2-phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S) -5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-
         isopropyl-1'-(4-carboxamidoimidazol-2-yl)]methyl-6-phenyl-2-
         phenylmethyl-hexanamide;
         (2R, 4S, 5S, 1'S)-2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-
         thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
        yl))methyl-hexanamide;
         (2R, 4S, 5S, 1'S) -2-phenylmethyl-4-hydroxy-5-(5-(1-oxopropyl)-2-
        thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
'Then 'yl))methyl-hexanamide;
.f. ad: 30 iou (2R, 4S, 5S, 1'S).-2-phenylmethyl-4-hydroxy-5-(5-propyl-2-
        thiazolyl)amino)-6-phenyl-N-(1'-isopropyl-1'-(imidazo-2-
        yl))methyl-hexanamide; and Jumile' is become on the 1812 to
        (2R, 4S, 5S, 1'S)-5-(nicotinyl) amino-4-hydroxy-N-(1'-isopropyl-
        1'-imidazol-2-yl) methyl-6-phenylmethyl-hexamide.
```

11. A compound according to claim 1 which is (2R, 4S, 5S, 1'S) -. 5-(t-butoxycarbonyl) amino-4-hydroxy-N-[1'-isopropyl-1'-(4-

12. A compound according to claim 1 which is (2R, 4S, 5S, 1'S) 
2-phenylmethyl-4-hydroxy-5-(t-butoxycarbonyl)-amino-6-phenyl
N-(1'-isopropyl-1'-(imidazo-2-yl))methyl-hexanamide.

The contract of the contract o

according to Claim 1 and a pharmaceutically (acceptable carrier.

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14. A pharmaceutical formulation comprising a compound according to Claim 1 and an oil 3 -2 - (12. 32. 32.)

(Edge Syde) of the constant of

15 15. A method of treating disease states associated with HIV infection comprising administering an effective amount of a compound according to Claim 1.

Commercial of the property of the second of

16. The use of a compound according to Claim lain the manufacture of a medicament.

The Control of the State of the popular state of the stat

17. A compound of the formula: A AND of the party of

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and the second second second second

wherein Pr2 is an amino protecting group, and R7', R8' and R9' are as defined in Claim 1 with any greactive groups protected.

30 18. A compound of formula: as to be the wardy to be a first married

$$R_1$$
  $R_2$   $R_3$   $R_4$   $R_5$   $R_6$   $R_6$   $R_8$   $R_8$   $R_8$   $R_8$   $R_8$   $R_8$   $R_8$   $R_8$   $R_8$ 

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wherein:

R<sub>1</sub> and R<sub>3</sub> are each independently C<sub>1-6</sub>alkyl,
Ar\_C<sub>1-6</sub>alkyl, Het-C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, Ar-C<sub>2-6</sub>alkenyl,
Het-C<sub>2-6</sub>alkenyl, C<sub>3-6</sub>cycloalkyl-C<sub>1-6</sub>alkyl or
C<sub>3-6</sub>cycloalkenyl-C<sub>1-6</sub>alkyl;

THROUGH OF OH; HE THE TO SEE THE TELEPHONE

wherein:

10

X is NR<sub>11</sub>, O, or S,

O!R11iis H:or C1\_3alkyl; ()

YURg and Rg are each independently H, OH, halo, acyl,

or substituted alkyl;

15 wherein:

X is NH, O, or S;

moiety; State of the state of t

 $R_7$  is  $C_{1-6}$ alkyl,  $Ar-C_{1-6}$ alkyl,  $Het-C_{1-6}$ alkyl,

20 C2-6alkenyl, Ar-C2-6alkenyl, Het-C2-6alkenyl,

60 C3\_6cycloalkyl-C126 alkyl or C3\_6cycloalkenyl-C1\_6alkyl;

 $R_{10}$  is a molety: A-(B)<sub>n</sub>-, where n = 0 or 1; and B is, independently, an  $\alpha$ -amino acid chosen from the group: Ala,

Asn, Cys, Trp, Gly, Gln, Ile, Leu, Met, Phe, Pro, Ser, Thr,

25 Tyr, Val, His, or trifluoroalanine, wherein the amino group of B is bonded to A and the carboxy group of B is bonded to the structure;

A is covalently attached to the amino group of the active adjacent residue B or to the amino group of the structure if

- 1) trityl,
- 2) hydrogen,
- to plan (43) The Ciifalkyl, include the con-
  - 4) R14-CO-wherein R14 is:

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		- a)	hydr	rogen, it is the two countries and the	
• • •	•: • •	b)	C1-68	alkyl, únsubstituted or substituted	with
		:	one	or more hydroxyl groups, chlorine at	toms,
			or f	fluorine atoms, holymetisoft 19, .co	
. 5		c)	phen	yl or naphthyl unsubstituted or	•
•	*	•	subs	tituted with one or more substituent	s .R <u>1</u> 5
			where	rein R15 is:	
		-	i)	C1-4alkyl,	
			11)	halogen, where halogen is F, Cl, B	or
10	. •			and the second of the second o	
•			iii)	hydroxyl,	
•			iv)	nitro,	
			v)	C1-3alkoxy, or the talk at the case	
				-CO-N(R16)2, wherein R16 is,	
15	: •		inder	pendently, H or C1-4alkyl; or	
		d)	a 5-7	7 member heterocycle such as pyridyl	
	٠		furyl	l, or benzisoxazolyl;	
	5)	phth	aloyl	wherein the aromatic ring is	
				ited or substituted with one or more	
20		subs	tituen	nts R <sub>15</sub> ;	
.,	6)	ER17 (	R18R19	C) $m$ -CO- wherein $m$ = 1-3 and R17, R	18,
				e independently:	
•	i į			ogen, and the company of the company	
•	=			ine orafluorine) va com to a que o	
25		. c)	C <sub>1-3</sub> a]	lkyl unsubstituted for substituted wi	th
J. B. Gr	· · .	•	one o	or more chlorine or fluorine atoms or	
		-	hydro	xyl groups, and all pale as as assign.	
	•	d)	hydro	and the control of th	
				lyor naphthyleunsubstituted organical	
10 <sub>12: 13</sub> -	1 4	. •	subst	ituted with one or more substituents	R15,
•	•	£)	C <sub>1-3</sub> al	lkoxy,	•
		g). ·	a 5-7	member heterocycle, or	•
		<b>h</b> )	R17, F	R18, and R19 may be independently jo	ined
•	•		to for	rm a monocylic, bicyclic, or tricycl	e ·
5			ring s	system each ring of which is C3-6	
	:	•	cycloa	alkyl; as order to	<b>અ</b> ,
	7)		_	C) <sub>m</sub> -W- wherein $m = 1-3$ and W is OCO (	
		SO <sub>2</sub> a	nd R17	7. R18, and R19 are as defined above	•

except R17, R18, and R19 are not chlorine, fluorine or hydroxyl if they are adjacent to W;

- as pyridyl, furyl, or benzisoxazolyl;
- 9) R21-W- wherein R21 is phenyl or naphthyl unsubstituted or substituted with one or more subsituents R15;
- 10) R17-(R18R19C)m-P(0) (OR22) wherein R22 is C1-4 alkyl or phenyl;
  - 10 11) R<sub>20</sub>-P O) (OR<sub>22</sub>)-; or
    - 12) R<sub>21</sub>-P(0)(OR<sub>22</sub>)-;

or pharmaceutically acceptable salt thereof.

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# INTERNATIONAL SEARCH REPORT

PCT/US92/06047

	SSIFICATION OF SUBJECT MATTER				
	:CO7D 233/64, 263/32, 277/30; A61K 31/415, 3				
According t	to International Patent Classification (IPC) or to b	oth national classification and IPC			
B. FIEL	DS SEARCHED				
Minimum d	ocumentation searched (classification system follo	wed by classification symbols)			
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Documentati	ion searched other than minimum documentation to	the extent that such documents are included in	the fields searched		
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Electronio di	ata base consulted during the international search	(name of data base and, where practicable, so	arch terms used)		
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C. DOC	UMENTS CONSIDERED TO BE RELEVANT				
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Category*	Citation of document, with indication, where	appropriate of the relevant passages	Relevant to claim No.		
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Further	documents are listed in the continuation of Box	C. See patent family annex.	:		
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	ority date claimed ual completion of the international search				
		Date of mailing of the international search r	chor		
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# INTERNATIONAL SEARCH REPORT

International application No. PCT/US92/06047

A. CLASSIFICATION OF SUBJECT MATTER: US CL:

514/19, 365, 370, 377, 392, 397, 398, 400; 546/175, 278; 548/193, 194, 200, 204, 233, 236, 312.7, 315.1, 328.5, 332.5, 338.1, 338.5

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

514/19, 365, 370, 377, 392, 397, 398, 400; 546/175, 278; 548/193, 194, 200, 204, 233, 236, 312.7, 315.1, 328.5, 332.5, 338.1, 338.5